JAN 12 1931

VOLUME 22 NUMBER 1

ARCHIVES OF SURGERY

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JANUARY, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 22 JANUARY, 1931 NUMBER 1

PERITONITIS

I. THE CORRELATION OF THE BACTERIOLOGY OF THE PERITONEAL EXUDATE AND THE CLINICAL COURSE OF THE DISEASE IN ONE HUNDRED AND SIX CASES OF PERITONITIS *

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NEW YORK

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* Submitted for publication, April 28, 1930.

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The important surgical problem of peritonitis has held the attention of hosts of clinicians and laboratory investigators for many years, and the reports of their observations are abundant. The publications of the last few years bear witness to the fact that there are today many workers in the field of investigation of this disease. Nevertheless, we make no apology for joining them in an effort to elucidate this problem further, for the disease is the bête noir of the abdominal surgeon and yearly takes its heavy toll of life. We believe that any presentation of accurate observations, if correlated with the observations of others, will help in the eventual solution of the problem.

Peritonitis has been studied from many different angles. Clinical observations of the varied manifestations of the disease were, of course, the first to be reported. Later, anatomic and physiologic features were disclosed. With the advent of bacteriology, peritonitis offered a wide and bewildering field of research, as indicated by the numerous reports of studies made in the last decade of the last century and in the first decade of the twentieth. Of recent years, the chemical aspects of the disease have been intensively studied, and there has been a growing knowledge of the profound disturbance of chemical balance that takes place during the progress of this disorder, particularly when it is complicated by intestinal obstruction. Of late also, there has been renewed interest in the immunologic and serologic factors that play a part in the recovery from this grave disease, and in the prevention of its development.

About five years ago, we elected to attack the problem from the immunologic and serologic side, but we felt that to do so intelligently we should first have to review the older studies in bacteriology and make certain preliminary bacteriologic observations of our own to see if the more recent methods of bacterial cultivation, particularly of the anaerobic organisms, would yield results fundamentally different from those already reported. We spent some time, therefore, developing the technic of anaerobic culture and studying the pathogenic anaerobes which have received so much attention from bacteriologists since the World War. We have studied particularly the intestinal organisms of man and laboratory animals, both aerobic and anaerobic, and those found in raw "catgut," because of the frequency of perforation of the intestine as an antecedent to the development of peritonitis.

The earlier studies of the bacteriology of peritonitis were made with an imperfect understanding of the requirements for growth of the anaerobic bacteria. The simple methods and even some of the elaborate methods that were used were not adequate to bring to light anaerobes that were frequently seen on smear, but not cultivated, and it is not surprising that at first emphasis was placed on the more easily growing organisms. The literature on this subject is voluminous. It would not

be profitable to attempt a complete compilation of the published reports, but, in order that we may compare our own results with those previously set forth, we shall review briefly those articles which seem to us to be representative of the best work that has been done in this field.

LITERATURE

In 1879, Grawitz [1] reported his studies in peritonitis, pointing out that there was a group of primary infections of the peritoneum and another group that was secondary to other lesions on the one hand, those which seemed to arise as a disease entity of the peritoneum itself and, on the other, those which developed by contiguity from disease of the intra-abdominal organs.

Pawlowsky was among the first to study peritonitis experimentally, and reported his work in 1887.[2] He injected croton oil and found that it produced a hemorrhagic exudate. Trypsin produced a high degree of inflammation and even 0.25 Gm. caused death in experimental animals. Contents of the small intestine injected into the peritoneum produced a fibrinopurulent peritonitis from which he cultivated a small bacillus. When this was injected in pure culture, death or recovery depended on the dosage. If intestinal contents were filtered, the filtrate would not kill, or if it was sterilized by heating on eight successive days at 55 C., it had no effect. Pawlowsky concluded that the intestinal bacteria were the prime factors in peritonitis, and the chemical ferments played a secondary rôle.

In 1890, Bönnecken [3] made a bacteriologic study of the sac fluids in cases of strangulated hernias. He observed eight human cases and a series of experimental cases in dogs in which he produced an analogous lesion by passing a loop of intestine through a rubber ring and covering the loop with a rubber bag. This was replaced in the abdomen and examined after given periods of strangulation or after death. If it was examined within from twelve to eighteen hours, the fluid was usually clear; if the strangulation was particularly tight or the duration longer, the fluid was found to be blood-tinged or dark brown, turbid and flocculent. The appearance of the wall of the intestine varied from light venous hyperemia to hemorrhagic infiltration or frank necrosis. Bönnecken made cultures, not only of these fluids,

1. Grawitz, P.: Statitischer und experimentell-pathologischer Beitrag zur Kenntnis der Peritonitis, Charité-Ann. **11**:770, 1886.

2. Pawlowsky, A. D.: Beiträge zur Aetiologie und Entstehungsweise der akuten Peritonitis, Centralbl. f. Chir. **14**:881, 1887.

3. Bönnecken, H. B.: Ueber Bakterien des Bruchwassers eingeklemmter Hernien und deren Beziehung zur peritonälen Sepsis, Virchows Arch. f. path. Anat. **120**:7, 1890.

but of the contents of the strangulated loops and the wall of the intestine as well. He found that the organisms in the fluid could also be found inside the intestine, and concluded that they passed through the wall. In several of these cases, including one human case in which the strangulation had lasted only four hours, the wall of the intestine showed only a high degree of venous hyperemia, and yet the fluid contained numerous bacteria. He found *B. coli* in eleven of fifteen cases and other bacilli which he briefly described but did not name. There were also several different kinds of streptococci and staphylococci. No anaerobic cultures were made, and it is probable that even in mixed cultures he failed to observe any anaerobes. He felt that his cases clearly showed that there did not need to be very great changes in the wall of the intestine for the intestinal bacteria to pass through.

A year later, in 1891, Malvoz[4] reported a study of peritoneal exudates at autopsy, and said that he agreed with Laruelle[5] that peritonitis of intestinal origin should not be attributed to any organism except *B. coli*. Malvoz found it in pure culture in a case of perforated gallbladder, in a case of perforated ulcer of the stomach and in a case of obstruction of the rectum without perforation. It was combined with other organisms in a case of mesenteric thrombosis with gangrene and in a case of perforated typhoid ulcer. Malvoz thought that it could not be considered a secondary invader, because it is so rarely found as a contaminant in cases of streptococcus or pneumococcus peritonitis. Laruelle found *B. coli* in pure culture in two cases of perforated appendix. When he injected *B. coli* into animals, he found that he could produce peritonitis, but that the lesion was more like that in human beings if he injected bile or sterile intestinal fluid along with the organisms. Laruelle, and Malvoz both agreed, however, that *B. coli* is often present without perforation, and therefore the intestinal fluid is not necessary for the production of peritonitis. The question arises, do we know that intestinal juices do not pass through an inflamed wall as well as bacteria?

De Klecki,[6] recognizing the intestinal origin of the organisms found in peritonitis, vouchsafed the opinion that the intestinal bacteria increase in virulence before or as they enter the tissues of the wall of the intestine. As time went on, various workers added to the list of

4. Malvoz, E.: Le bacterium coli commune comme agent habituel des péritonites d'origine intestinale, Arch. de méd. exper. et d'anat. path. **3**:593, 1891.

5. Laruelle, L.: Étude bacteriologique sur les péritonitis par perforation, Cellule **5**:61, 1889.

6. de Klecki, C.: Recherches sur la pathogénie de la péritonite d'origine intestinale. Étude de la virulence du colibacille, Ann. de l'Inst. Pasteur **9**:710, 1895.

bacteria found in peritonitis. Jalaguier [7] added *Staphylococcus albus;* Fraenkel [8] added streptococcus, and Barbacci,[9] pneumococcus. Each one stressed the importance of the organism observed by him, and although *B. coli* was generally found, its significance was questioned because of its apparently benign state within the intestine.

The first comprehensive report from the earlier workers was the result of observations by Tavel and Lanz,[10] who, in 1893, carefully studied seventy-two cases and tried to correlate to some degree their clinical and bacteriologic observations. Although their methods were not adequate to recover many of the anaerobic bacteria, some of their observations are of particular interest and have been repeatedly confirmed. They divided their cases of peritonitis into five groups: (*a*) cases following lesions of the gastro-intestinal tract, (*b*) those following lesions of the gallbladder and liver, (*c*) those following lesions of the genito-urinary tract, (*d*) those following operative peritonitis and (*e*) those of hematogenous origin. They considered twenty-three cases yielding no bacteria on culture to be due to chemical irritants. Of the other forty-nine that yielded bacterial growth, fourteen gave a pure culture of a single species. The other thirty-five were "polymicrobic." *B. coli* was found in thirty of the forty-nine cases, and some form of streptococcus in twenty-eight. They distinguished three different forms of streptococci. No organisms similar to *B. aerogenes-capsulatus,* which had been reported the previous year (1892) by Welch and Nuttall,[11] were described. They found the cases with a single organism to be very diverse in nature, while the polymicrobic cases came largely from intestinal lesions. In the mixed infections they found it difficult to say which organism was the most important. When no organisms were present, the prognosis was good, and in the cases in which organisms were found, the polymicrobic infections gave a better outlook than the monomicrobic, but they could not find any correlation between the severity of the clinical symptoms and the number of species found in any given case. They observed that lesions of the small intestine were much more dangerous than

7. Jalaguier, M.: Résultats de l'examen bactériologique du pus d'une péritonite généralisée par perforation de l'appendice ileo-coecal, Bull. et mém. Soc. de chir. **18**:390, 1892.

8. Fraenkel, E.: Zur Aetiologie der Peritonitis, München. med. Wchnschr. **37**:23, 1890.

9. Barbacci, O.: Ueber Aetiologie und Pathogenese der Peritonitis durch Perforation, Centralbl. f. allg. Path. u. path. Anat. **4**:768, 1893.

10. Tavel, E., and Lanz, O.: Ueber die Aetiologie der Peritonitis, Mitt. a. d. Klin. u. med. Inst. d. Schweiz. **1**:1, 1893.

11. Welch, W. H., and Nuttall, G. H.: A Gas Producing Bacillus (B. aerogenes capsulatus nov. spec.) Capable of Rapid Development in the Blood-Vessels After Death, Bull. Johns Hopkins Hosp. **3**:81, 1892.

lesions of the large intestine and offered as a probable explanation that if perforation takes place in lesions of the small intestine, the contents of the intestine are so fluid that they spread around rapidly while the more solid contents of the large intestine are more apt to localize, to be less widely diffused.

Flexner,[12] in 1898, reported a postmortem bacteriologic study of one hundred and six cases of peritonitis. While he admitted the possibility of error because of postmortem invasion, he thought that this was inconsiderable. Postmortem reports have the further disadvantage that there is no consideration of those cases in which recovery occurred. So that whereas Tavel and Lanz in studying specimens from the operating room found twenty-three that yielded no bacteria and that they called cases of "chemical peritonitis," Flexner found very few that yielded no growth and thought that "chemical peritonitis" must be an extremely rare condition. He divided his cases into twelve primary and ninety-four secondary cases. The primary cases were mostly terminal infections in patients with various and sundry chronic disorders. The secondary cases he divided into thirty-four exogenous and sixty endogenous. In the exogenous group, he placed operative infections in wounds as well as traumatic genito-urinary lesions, and found that the bacteria in these cases corresponded to those usually found in wound infections, twenty-five of them yielding a single species and only nine more than one species. Of the sixty endogenous cases, two yielded no bacteria, twenty-one gave a single type of organism and thirty-seven gave multiple species. Of the thirty-seven multiple, thirty-four yielded two species, two had three species and one had four. "Anaerobic cultures were only made in exceptional cases"—he does not state why. And this is the more surprising because Flexner was associated with Welch in his studies with *B. aerogenes-capsulatus,* and in 1896 reported cases of peritonitis yielding this organism. In Flexner's series, *B. aerogenes-capsulatus* (*C. welchii*) was found only seven times. He brought out the fact that streptococci are much more common than staphylococci in cases of peritonitis of intestinal origin, but concluded that of all the organisms found, *B. coli* was the organism of greatest importance.

The reports thus briefly summarized represent the early observations that constitute the aerobic era of the bacteriologic knowledge of peritonitis. In 1896, a new epoch began when Welch and Flexner[13] reported seven cases of peritonitis yielding *B. areogenes-*

12. Flexner, S.: The Etiology and Classification of Peritonitis, Philadelphia M. J. **2**:1019, 1898.

13. Welch, W. H., and Flexner, S.: Observations Concerning the Bacillus aerogenes capsulatus, J. Exper. Med. **1**:5, 1896.

capsulatus. We are not sure whether these are the same seven that Flexner later reported in his large group, but appearing together as they do in the earlier report, they constitute the first series of cases that suggested the importance of the anaerobic bacteria in this disease. They found the organism in five perforative lesions of the intestine and in two nonperforative lesions. Two years later, in 1898, Veillon and Zuber [14] came out as the champions of the anaerobic hypothesis. They examined the exudate in twenty-two cases of appendicitis. They found anaerobes in twenty-one of these cases, twice in pure culture, and from their observations, drew these conclusions:

> Anaerobes are constantly found in the pus of appendicitis, in abscesses around the cecum, and in the peritoneal cavity in general peritonitis. . . . Their extreme abundance on smear, (?) their predominance over *B. coli* and other aerobes, and their existence in pure culture in certain of these cases, their pathogenic properties and chemical properties permit us to state that they play the principal rôle in the production of appendicitis. . . . Due to their gangrenous properties, some perforate the appendix and some give typical gangrenous pus. It is their toxins which give the symptoms to which patients often succumb.

They described five different kinds of anaerobic bacilli, among them *B. perfringens* (which was later identified as *B. aerogenes-capsulatus* and has since been named *C. welchii*) and an anaerobic coccus. This report obviously ignored the aerobic organisms in order to emphasize the anaerobic, and it called attention in a very emphatic manner to their presence, even though it went farther than the evidence indicated in estimating their importance.

In 1902, Friedrich [15] reported a study of perforative peritonitis in which both aerobes and anaerobes were described. *B. coli*, streptococci, *B. proteus*, *B. pyocyaneus* and staphylococci were found among the aerobes. Anaerobes were isolated from almost every peritoneal exudate. He does not describe them further than to say that the bacilli were generally of the malignant edema or tetanus types, and that there were also anaerobic streptococci. Thus Friedrich confirmed to some degree the work of Veillon and Zuber and at the same time recognized the rôle played by the aerobes, although he failed to give statistics and did not clearly indicate his opinion of their relative importance.

In 1904, Lanz and Tavel,[16] having had the anaerobes called to their attention by reports that followed their earlier one,[11] published another

14. Veillon and Zuber: Recherches sur quelques microbes strictement anaérobies et leur role dans la pathologie humaine, Arch. d. méd. expér. et d'anat. path. **10**:517, 1898.

15. Friedrich, P. L.: Zur bacteriellen Aetiologie und zur Behandlung der diffusen Peritonitis, Arch. f. klin. Chir. **68**:524, 1902.

16. Lanz, O., and Tavel, E.: Bactériologie de l'appendicite, Rev. de chir. **30**: 43 and 215, 1904.

series in which they compared the bacteriologic flora found in the contents of normal appendixes, diseased appendixes and appendiceal abscesses to see whether there was any correlation between the bacterial content and the pathologic state. In this report they differentiated between *Streptococcus pyogenes* and the other intestinal streptococci. They also subdivided the anaerobes, giving the bacillus of malignant edema and the pseudotetanus bacillus the most important places numerically. They included in the malignant edema group *B. perfringens* of Veillon and Zuber and *Vibrion septique* of Pasteur. Their group of normal appendixes was small, only eight specimens being studied, whereas there were one hundred and thirty-eight diseased appendixes. In the normal appendixes, *B. coli* was found in 100 per cent, *Streptococcus pyogenes* in 25 per cent, diplostreptococci in 37.5 per cent, malignant edema bacilli in 62.5 per cent and pseudotetanus in 45.4 per cent. Over 10 per cent of the diseased appendixes yielded no growth. This they thought to be due to the emigration of leukocytes and the phagocytosis of the bacteria. They stated:

> The qualitative analysis confirms our ideas. One would expect to find more pathogens and less saprophytes in the pathologic appendices than in normal. It is seen that the streptococci and diplococci are increased, while the coli, the malignant edema, and the pseudotetanus groups are less, but as there was no way of determining the virulence of these organisms for man, we cannot draw any definite conclusion.

In spite of these reports of anaerobes as factors in the disease, a number of later observers published the results of studies that minimized the anaerobes or ignored them entirely. It is quite evident that they either made no effort to find them or that their technic was not adequate to recover them. For example, in 1903, Manahan,[17] who studied nineteen cases of peritonitis to determine the presence of bacteria in the fibrin clinging to the wall of the inflamed intestine, made smears of the exudate and cultivated it. In three cases he saw organisms resembling *B. aerogenes-capsulatus* of Welch in the smear and in the fibrin, but they failed to grow with "Wright's anaerobic method." Later, in 1905, when Manahan reported a bacteriologic study of a series of one hundred and ten cases of peritonitis at autopsy, he included only one case that yielded the Welch bacillus. He emphasized the importance of the streptococci, for he found them in pure or mixed culture in fifty-four of the eighty-nine cases in which a bacteriologic examination was made, while *B. coli* was present in only forty-five.

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17. Manahan, T. J.: Bacteriology of the Fibrinous Exudate in Septic Peritonitis, J. M. Research **9**:445, 1903; The Bacteriology of General Peritonitis, Boston M. & S. J. **152**:346, 1905.

In 1905, Kelly,[18] in the book on the appendix and its diseases, gave a summary of the literature on the bacteriology of appendicitis, including those articles which stressed the rôle of the anaerobes. However, in the figures that he gave for the incidence of the various organisms, he used some older statistics from the Johns Hopkins Hospital, in which the anaerobes were obviously neglected—the chief importance being attributed to *B. coli,* streptococcus and staphylococcus.

Similarly, in 1905, Dudgeon and Sargent [19] published a monograph of considerable length in which some careful observations are recorded, but their bacteriologic results are so at variance with those of other observers, that it seems to be necessary to conclude that their methods were at fault. A few quotations will illustrate this: "There does not appear to be any constant relation between the length of the history of the illness and the bacteriological findings." They "failed to find any evidence to show that anaerobic organisms are of any importance in appendicitis." They stated that "the bacteriology of the pus from a localized abscess is of little clinical interest, being practically the bacteriology of the intestinal contents." Only one case of appendical abscess yielded the Welch bacillus, and they concluded that "if this were frequently present in the peritoneal cavity—emphysematous gangrene of the bowel should be a common lesion but it is not." They believed that staphylococci play the most important rôle in the bacteriology of appendicitis. They found *Staphylococcus albus* in all parts of the peritoneal cavity, often in pure culture from normal or relatively normal peritoneal surfaces far from the main lesions or in areas where there was no evidence of inflammation. They found it also in blood clots, in ectopic pregnancy or hemorrhagic injuries and in conjunction with other organisms in various lesions. We have no adequate explanation for their results, and they themselves said, "How or why the staphylococcus albus appears, we are unable to hazard a guess." It is possible that in some instances at least they confused *Staphylocccus albus* with some of the intestinal streptococci that they did not mention as such. We have felt it necessary to dwell at length on this, because the work of Dudgeon and Sargent is often quoted as being authoritative.

In 1908, Runeberg [20] made an intensive study of fifteen cases of peritonitis of appendical origin. His report covers three hundred and

18. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905, p. 489.

19. Dudgeon, L. S., and Sargent, P. W. G.: The Bacteriology of Peritonitis, London, Constable & Company, 1905, p. 243.

20. Runeberg, B.: Studien über die bei peritonälen Infektionen appendikulären Ursprungs vorkommenden sauerstofftoleranten sowie obligat anaëroben Bakterienformen, mit besonderer Berücksichtigung ihrer Bedeutung für die Pathogenese der artiger Peritonitiden, Arb. a. d. path. Inst. Univ. Helsingfors **2**:271, 1908.

eleven pages and deals elaborately with the literature, with his technic, with a detailed description of the organisms which he recovered, with case reports and with a discussion of his results. In four of his cases an abscess had formed. Three of these were opened and drained without removal of the appendix. In all of the other cases the appendix was either partially or completely gangrenous. In four of these cases there was no gross perforation. In the exudate from one of these four no viable organisms were found, and one yielded a pure culture of an intestinal streptococcus. The other two nonperforative cases and all of the perforative cases, as well as the cases of abscess yielded abundant bacterial growth. *B. coli* was present in all but one case (abscess), and gram-negative nonspore-forming anaerobes in all but three. Intestinal aerobic streptococci, anaerobic gram-positive nonspore-forming bacilli and anaerobic cocci occurred in lesser frequency. *C. welchii* (*B. perfringens, B. aerogenes-capsulatus*) was not found in the peritoneal exudates, but was recovered once from the contents of the appendix. Runeberg made no effort to correlate the bacterial observations with the course of the disease. He stated in his summary that "no single form found in peritonitis following gangrenous appendicitis with or without perforation was shown to be able to escape into the peritoneal cavity and multiply there earlier than any other form. Therefore no single bacterial cause of peritonitis was shown." Although *B. coli* was the commonest organism present, the anaerobes generally exceeded the aerobes in number, but none of these anaerobes was found to be pathogenic. A study of the patients' serum for agglutinins seemed to show more reaction to the anaerobes than to *B. coli* or the streptococci.

In 1909, Kotzenberg [21] essayed to determine whether or not *B. coli* was an invading organism or merely a secondary contaminant by testing the serum of patients ill with perforative appendicitis and peritonitis for increased opsonic power. In twenty-one cases, ten yielded *B. coli* in pure culture and the patients' serum showed an increased opsonic index to *B. coli*. In six cases in which *B. coli* was found with other organisms, the index was increased for *B. coli* but not for the others. In three cases with *B. coli* and *Streptococcus*, and in one case with *B. coli* and *Staphylococcus*, the index was increased in both. In another with *B. coli* and *Staphylococcus* it was increased for the staphylococcus but not for *B. coli*. These results seemed to the author evidence that the body was reacting to the invasion of these organisms and that they were in fact active in the infection. The difficulty of evaluating the opsonic index in any particular series of cases, and the

21. Kotzenberg: Zur Therapie und Bakteriologie der eitrigen Perforations-Peritonitis, Deutsche med. Wchnschr. **35**:201, 1909.

necessity for adequately controlling results of this kind with normal persons, is obvious. This was not done adequately by Kotzenberg.

In 1911, Heyde [22] published an excellent article based on clinical observations and painstaking laboratory studies. He reviewed the literature up to that time thoughtfully and critically and appears to have had a clear understanding of the whole problem. He obtained material for bacteriologic examination from one hundred and two patients. The lesions were classified as those of purulent appendicitis, gangrenous appendicitis, peritonitis of appendical origin, abscess and interval or chronic appendicitis. He examined by smear and culture the contents of the removed appendixes, the peritoneal exudates and in a few cases the pus from secondary abscesses. He showed the correlation of the bacteriologic observations of the different fluids in the individual cases but made no effort to correlate these observations with the clinical course of the disease. His clinical groups overlap to a considerable degree, particularly in the gangrenous appendicitis, peritonitis and abscess groups. It is not clear which of his patients had perforative lesions and which did not. He stated that most of the lesions were perforative. Furthermore, in his tables he did not distinguish between the flora of the contents of the appendix and of the peritoneal exudates. By going through his case reports and selecting the results of his study only with regard to the peritoneal exudates, which seem to us to be infinitely more important than the contents of the appendix, we have been able to obtain data that we can compare with our own, particularly with regard to the bacteriologic studies. Heyde was manifestly in search of the anaerobes. He used the methods of von Hibler and others of his own which were chiefly designed to avoid the prolific growing propensities of *B. coli,* which was so commonly present that it gave him all sorts of trouble. He depended chiefly on dilution tube cultures in solid or semi-solid mediums. Even though it was by far the most frequent organism found, Heyde considered that *B. coli* played a subordinate rôle in the etiology of appendicitis. Of considerably more importance, in his opinion, is the small gram-negative nonspore-forming anaerobic organism *B. thetoides,* which is the same as Veillon's and Zuber's *B. fragilis.* He could not demonstrate its pathogenicity. He found it difficult to separate this bacillus from *B. coli* in the undiluted specimens, but by diluting them down through a series of agar tubes, which solidified after seeding, he was able after incubation to pick out the colonies of this organism. In the forty-nine peritoneal exudates that he examined, he found *B. thetoides* in about 45 per cent and *B. coli* in about 60 per cent. He

22. Heyde, M.: Bakteriologische und experimentelle Untersuchungen zur Aetiologie der Wurmfortsatzentzündung (mit besonderer Berücksichtigung der anaëroben Bakterien), Beitr. z. klin. Chir. **76**:1, 1911.

found *B. aerogenes-capsulatus* (*C. welchii*) in about 15 per cent, while other spore-forming anaerobes, which he classified as bacilli of the malignant edema and of the pseudotetanus groups, were present to a lesser degree. Certain nonspore-forming, gram-positive rods (*B. ramosus* and *B. ramosoides*) were present in from 15 to 25 per cent, and several of these were found in pure culture. An organism which he called the parapneumococcus was present in almost 25 per cent of his cases, while anaerobic streptococci were found in 20 per cent of the cases. Heyde's experiments on animals were limited in number, and although he found them to be consistent, his results were not sufficiently striking to repeat here. His final conclusions with regard to the clinical cases were as follows:

1. The anaerobic organisms, in all stages of appendicitis and the peritonitis arising from it occur in the greatest variety and number.

2. They invade the peritoneum more quickly than the aerobes and spread themselves over the serosa without being accompanied by the aerobes.

3. There seem to be particular kinds of organisms present in particular conditions of infection which have a particular etiologic significance.

In going over his results, it does not seem to us that Heyde is justified in making these sweeping statements. We feel that his interest in the anaerobes led him not to give full credit to the aerobes. Heyde's results differ from the ones that we shall report, chiefly in the incidence of the small gram-negative anaerobic bacillus, *B. thetoides,* which we found in only three cases. On the other hand, his incidence of *B. coli* is low compared with ours, particularly as his cases were largely perforative. We found *B. coli* in almost every instance with a perforative lesion. While it is conceivable that this prolific gram-negative anaerobic *B. coli* may easily hide the slower growing gram-negatve anaerobc *B. thetoides,* it does not seem likely that the anaerobe would be confused with *B. coli,* nor does it seem likely that these organisms would be mistaken for one another when they were once isolated. Therefore, we must grant that Heyde's results are probably accurate for his series, and we shall endeavor to evaluate the importance of this organism in our further studies.

In 1912, Fishbein [23] reported some postmortem bacteriologic studies which largely confirm the previous work by Manahan and by Flexner, and although he refers to Heyde and other students of the anaerobic organisms, he states that anaerobic cultures were usually not made in his series.

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23. Fishbein, M.: Contribution to the Bacteriology of Peritonitis with Special Reference to Primary Peritonitis, Am. J. M. Sc. **144**:502, 1912.

Wilkie,[24] in 1912, emphasized the advisability of the surgeon examining microscopically in the operating room smears from the peritoneal fluid in cases of diffuse peritonitis in order to have a basis for deciding the question of drainage and for making a prognosis in any given case. His belief was that if the polymorphonuclear leukocytes showed active phagocytosis, and particularly if these cells were found ingested by macrophages, recovery was assured and drainage was usually unnecessary. Wilkie believed that this was more important than cultural studies because of the time required to complete them.

In 1915, Carslaw [25] carried this idea further and went into fine distinctions of cellular differentiation and into the question of cellular disintegration. Carslaw, in general, confirmed Wilkie in the matter of phagocytosis, but said that he thought phagocytosis of bacteria was more important than phagocytosis of cells. He believed that the duration of the disease had to be considered; for example, the absence of polymorphonuclears early in the course of the disease was not surprising, but if absent late in the course, the prognosis was bad. On the other hand, early degeneration of polymorphonuclears was bad and late degeneration was to be expected. Carslaw did not agree with Wilkie that the smear could give a basis for drainage, because that depended rather on the presence or absence of necrotic tissue.

Of recent years, there have been only two reports that warrant particular mention. One of these by Brütt,[26] in 1923, emphasizes the anaerobic streptococci. It seems likely that he included in this group certain micro-aerophylic streptococci that were not really anaerobes but which in the first few artificial transfers behaved as such. He considered without convincing proof that the anaerobic streptococci tend to produce thrombophlebitis, and thus bacterial gangrene and perforation.

In 1928, Weinberg and his associates [27] reported the results of studies carried out over a period of several years in the field of anaerobic bacteriology. During the war he was struck by the clinical similarity between cases in which the patients died of peritonitis following acute appendicitis and those in which they died of gas gangrene. He suspected that this was due to the rôle played by the anaerobes in both of these diseases.

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24. Wilkie, D. P. D.: Prognostic Value of an Immediate Examination of Peritoneal Exudates, Internat. Clin. **4**:145, 1912.

25. Carslaw, R. B.: On the Character, Significance and Prognostic Value of Peritoneal Exudates, Brit. J. Surg. **3**:8, 1915-1916.

26. Brütt, H.: Die Bedeutung der anaëroben Streptokokken für die destruktive Appendicitis, Beitr. z. klin. Chir. **129**:175, 1923.

27. Weinberg, M.; Prevot, A. R.; Davesne, J., and Renard, C.: Recherches sur la bactériologie et la sérothérapie des appendicites aigues, Ann. de l'Inst. Pasteur **42**:1167, 1928.

In referring briefly to the literature of the bacteriology of appendicitis, Weinberg spoke of the aerobic epoch and the anaerobic epoch and suggested that the pendulum has swung too far in giving the anaerobes almost exclusive responsibility in the etiology of appendicitis. Weinberg did not mention specifically the work of Heyde, though he doubtless knew of it. Weinberg's material, though more voluminous, was not as comprehensive as Heyde's, because the latter examined peritoneal exudates as well as appendical contents, while Weinberg did not.

Acute and gangrenous appendixes were sent to Weinberg's laboratory in sterile containers from various hospitals in Paris and were examined "usually the same day." They were placed in a Petri dish and with fine scissors opened from end to end the laid out flat. To quote from their report: "The pathologic exudate from the level of the lesion was sucked up into a sterile pepette, taking care to avoid fecal material and fecoliths so as to eliminate their flora and study exclusively the bacteriology of the specific lesions of acute appendicitis." This technic is subject to grave criticism, for it is inconceivable that it would be possible to avoid cultivating intestinal organisms that were only casually and not causally present at the site of the lesion on the interior of an appendix that had been opened from end to end. However, by passing this material through a series of dilutions of solidifying culture mediums to a point where, after incubation, individual colonies could be fished, those organisms which were present only in small numbers would largely be eliminated, and only those presumably most active at the site of the lesion would be recovered. One could not be sure, however, that the organisms in greatest number were necessarily causative or even active in the lesion. With these conditions in mind, one must discount to some degree the statistics which Weinberg and his co-workers present, and yet we believe that his results have considerable significance. Weinberg studied one hundred and sixty acutely inflamed appendixes, fifty-eight of which were gangrenous. He does not state how many of the gangrenous appendixes had perforated. From the material removed from these lesions he obtained pure cultures of single species in nineteen cases. This is surprising and is perhaps indicative of the efficacy of his technic. In 49 cases he found two species; in 47, three; in 23, four; in 16, five; in 4, six; and in 2, seven. Altogether there were 264 aerobes and 204 anaerobes. Of the aerobes, *B. coli* was found in 85 per cent of the cases. The enterococcus group was found in 30 per cent of cases while other aerobic bacteria occurred much more rarely. *B. perfringens* (*C. welchii*) was found in 33 per cent of cases. Anaerobic gram-negative bacilli and anaerobic cocci were present in 39 and 19 per cent, respectively. Although the aerobes outnumbered the anaerobes in the whole series, the anaerobes predomi-

nated in the gangrenous cases, and Weinberg concluded that the gangrene was due to their presence. He found the *B. coli* strains and the *C. welchii* strains to be pathogenic for laboratory animals, but the other frequent organisms, namely, the enterococci, the gram-negative anaerobes and the anaerobic streptococci were for the most part innocuous when injected in pure culture. In association with the others, however, his experiments seem to indicate that they either became pathogenic or enhanced the power of the associated organisms. Although he was handicapped by having no measure of the effect of the enterococcus alone and the results are therefore not conclusive, the experiments suggest that the symbiotic action of the organisms found in these lesions produce an effect which they cannot produce singly. Weinberg expressed the belief that the production of gangrene is largely a symbiotic effect of two or more organisms even though he was not able to demonstrate this conclusively. He did not indicate which of the anaerobes present beside *C. welchii* play a rôle in this symbiotic action, although he implicated the gram-negative bacilli because of their prevalence.

BACTERIOLOGIC METHOD

MATERIAL AND TECHNIC

It seemed to us more rational in studying peritonitis to examine the material actually present in the peritoneal cavity and presumably left behind, to some extent at least, after operation, rather than to examine either the contents or the wall of an organ that had been removed from the patient and was no longer a factor in his illness. We, therefore, centered our attention almost exclusively on the peritoneal exudate. The whole surgical staff cooperated with us in this study. Some of the patients were our own. Most of them, however, were under the care of other surgeons in our clinic, although one of us was frequently present at the operation as an observer. As soon as the peritoneum was opened and it was seen to have an excess of fluid, as much as possible was taken up in a sterile syringe. If the fluid was present in relatively small quantities, two sterile cotton swabs were saturated with the fluid. If the operation occurred during the day, these specimens were for the most part taken directly to the laboratory; if the operation had been performed at night, the specimens were placed on ice and examined in the morning. It was thought that the delay of a few hours before examination would make a great difference in the results of culture, but such was not found to be the case. There was no appreciable difference between the day and night cultures. The specimens were sent or taken to the laboratory accompanied by a slip stating the duration of the symptoms, the diagnosis, the description of the fluid as to turbidity and consistency, quantity, location and odor, the description of the appear-

ance of the peritoneum and whether or not any perforation was present. In the large majority of cases, smears were made from the fluid before inoculation on glass slides for direct staining. When the specimens consisted simply of two saturated swabs, these were streaked directly on a pair of 5 per cent sheep's blood agar Petri plates and then broken off and a whole swab introduced into each of two cooked meat medium tubes containing 0.2 per cent dextrose and of p_H 7.6, one of which had been prepared to receive anaerobic cultures by preliminary boiling to drive off the contained air. When a large quantity of exudate was available, two meat tubes were inoculated with from 0.1 to 0.5 cc. and a large drop smeared on the surface of each of two blood agar plates. One plate and one tube were then incubated aerobically and the others anaerobically in a modified McIntosh and Fildes jar.[28] The tubes and plates were examined next day, but if there was no growth the incubation of negative cultures was continued for four or five days or longer. Occasionally, growth would appear in the second twenty-four hours and not in the first, but in our series, cultures that were negative after forty-eight hours remained so. When growth appeared on the plates, colonies were fished and identified in the usual way by morphologic and cultural studies. When the tubes showed growth they were plated and transfers made to fresh mediums in tubes which were heated to 70, 80 or 90 C., for fifteen minutes to destroy the nonspore-formers and qualitatively select the spore-formers. Colonies growing on the anaerobic plates were repeatedly plated both aerobically and anaerobically so as to determine their purity and their anaerobic requirements. We classified as anaerobes only those which would grow solely on the anaerobic and not on the aerobic blood agar plate after four or five transfers, except in the case of *C. welchii,* which can usually be identified after one or two transfers.

ADVANTAGES OF THE TECHNIC

We consider the anaerobic jar, with a replacement of the oxygen by hydrogen, to be ideal for anaerobic cultures because with it, any mediums that can be used aerobically may be used anaerobically. An indicator adequatedly checks the degree of anaerobiosis. Blood agar plates not only favor those organisms which require some enrichment of medium but permit the growth of the hemophilic organisms and signal at once the presence of the hemolytic bacteria. We are certain that all of the known pathogenic spore-forming anaerobes grow well on these blood agar plates, and we have made countless observations of their cultural characteristics on this medium. The blood agar plates served not only

28. McIntosh, J., and Fildes, P.: A New Apparatus for the Isolation and Cultivation of Anaerobic Micro-Organisms, Lancet **1**:768, 1916.

to permit the growth of anaerobes but inhibited the exuberant growth of certain aerobes such as the gram-negative bacilli, which frequently overgrow other colonies aerobically. The 0.2 per cent dextrose cooked meat medium is particularly favorable for anaerobic as well as for aerobic organisms. The meat not only acts as a buffer, but contains peroxidase which permits certain strict anaerobes (e. g., *C. welchii*) to grow without sealing the medium or incubating it in the anaerobic jar. The strictest anaerobes, however, e. g., *C. novyi* (*B. oedematiens*) require the jar, and therefore in our study we always incubated the tubes in the deoxygenated environment. The meat medium is just as good as brain medium, for with putrefactive organisms the meat is attacked and becomes discolored. The direct inoculation of plates gives some idea of the relative numbers of viable organisms in the exudate, while on the other hand, the most prolific organisms soon predominate in the fluid cultures so that the plates made from the broth cultures give no indication of the relative numbers of organisms in the original specimen.

The cooked meat medium in every case received a heavier inoculation than the direct plates, and therefore, organisms were recovered frequently from the meat medium which did not appear on the first plates. The combined aerobic and anaerobic cultivation of each specimen, both on blood agar plates and cooked meat medium, and the later transfer from the cooked meat medium to other blood agar plates gave us several chances to recover both the aerobic and the anaerobic organisms in each case. On blood agar plates, the *C. welchii* colony is usually very easy to distinguish because of its outer zone of partial hemolysis. The results of the study as given below indicate fairly well, therefore, the occurrence of this anaerobe. *B. coli* is, of course, easily recovered because of its profuse growth and the large size of its colony. The streptococci, however, may frequently be missed, and the groups may be confused because of the variability of the size and the appearance of the colony, the property of methemoglobin formation and the anaerobic requirements. Some strains will grow only anaerobically on the first or second transplants, but will then grow aerobically. Some will grow on the blood agar plate without changing the blood for a generation or two and then will be frankly green. Many of the streptococci were green from the start, and a few of these, after a number of transplants, became slightly hemolytic.

LIMITATIONS OF THE TECHNIC

Although we consider the foregoing technic adequate for the isolation of most aerobes and all of the well known pathogenic anaerobes, even those that require the strictest anaerobiosis, we do not claim that

every species present in every peritoneal exudate was recovered. There may very well have been organisms that would not grow in any mediums that we used, and there may have been others the growth of which was inhibited by the presence of other species, or which were outgrown by them both on the plates and in the fluid mediums. By an examination of the thickest part of the growth on the plate as well as the isolated colonies, we were often able to demonstrate the presence of those slowly growing organisms if they were morphologically different from the organism which is overgrowing them. Then it was usually possible to isolate them by replating the culture. But organisms present in fewer numbers than the predominating organisms, if they were morphologically indistinguishable from them, may have been lost. For example, if a small gram-negative nonspore-forming anaerobic bacillus should be present in the same exudate with *B. coli* but in smaller numbers, it might be missed. If it were present in as great or greater numbers, the chances are greater that it would be picked up on the anaerobic plate which inhibits to a considerable degree the exuberant growth of *B. coli*. It is possible that our results do not adequately indicate the incidence of this group of organisms which Runeberg, Heyde and Weinberg found rather frequently. On the other hand, the spore-forming and the gram-positive organisms are not likely to be missed, and it is in this group that all of the anaerobic bacilli are found which up to the present are known to be pathogenic for man.

NOMENCLATURE

In this study we have aimed to make large bacterial groupings rather than to go into the minutiae of cultural variations which seemed to us to be without particular value. For example, we did not attempt to subdivide the *B. coli* group, although we observed that at least four of these subgroups were represented. With the streptococci, their variability on successive cultivation, as previously stated, made our division somewhat arbitrary, but it seemed worth while first to set apart the hemolytic group and the anaerobic group and then separate the green producing streptococci from the other nonhemolytic types. All small gram-positive rods were grouped together as aerobic diphtheroids while the larger gram-positive spore-forming aerobes fell into the *B. subtilis* group. Certain gram-negative aerobes, for example, *B. proteus* and *B. pyocyaneus* were fairly easy to separate from the *B. coli* group and were given their usual names.

The taxonomy of the anaerobic bacilli has recently been clarified by the persistent efforts of a number of workers, and the Society of American Bacteriologists has adopted the term *Clostridium* to denote the large group of anaerobic spore-formers. We have, therefore, used the

official term *Clostridium welchii* to denote the common gas bacillus, *B. aerogenes-capsulatus* of Welch or *B. perfringens* of Veillon and Zuber. The other pathogenic gas gangrene organisms, *C. oedematis-maligni* (*Vibrion septique*), *C. novyi* (*B. oedematiens*) and *C. oedematoides* (*B. sordellii*) were not found in our series, nor was *C. tetani*. The other oval central or subterminal spore-forming anaerobes, which were very few in numbers, have been placed in the *C. sporogenes* group, while the oval end spore-formers, have been placed in the *C. tertius* group. The gram-positive, nonspore-forming anaerobes have been grouped together as anaerobic diphtheroids, belonging in general to the *B. ramosus* group, while the gram-negative nonspore-forming anaerobes belong to the *B. fragilis* or *B. thetoides* group.

CLINICAL METHOD

In order to correlate the bacteriologic observations with the clinical course without bias, the records were examined and the data obtained from them at the end of the study and without reference to the bacteriologic results. Because of the emergency of operation in many instances, data which we would have liked to have were not on the clinical record. It was found that in some instances the absence of a specific symptom or sign probably meant that it was not present, for example, chill. In other instances, it probably meant that it was not elicited; for example, "rebound tenderness." This must be kept in mind when the incidence of these symptoms or signs are considered. The symptoms that we thought might be of some significance were the following: nausea, vomiting, fever, chill, diarrhea, constipation and obstipation. In the cases of appendicitis, we were anxious to know whether or not the development of the disease was typical, by which we mean the rather sudden onset of general abdominal or epigastric pain localizing after a time in the right lower quadrant. The physical signs that we thought might be important were: tenderness, rigidity, rebound tenderness, distention, mass, pelvic signs of tenderness or mass and the number of abdominal quadrants that were involved. The only laboratory examination considered for all cases was the white blood cell count. The severity of the case was judged from a consideration of the general appearance of the patient and the whole aspect of the case before operation. The operative observations with the pathologic diagnosis were recorded. The amount, character, location and odor of the fluid as described by the operator were noted. The procedure of the operator and the after-treatment, with particular reference to the use of serum, infusions or transfusions, were listed. The development of complications or serious sequelae, the duration of the stay in the hospital, the age of the patient and the final outcome were recorded.

PRESENTATION OF DATA

The most obvious results of the clinical review of these cases was the necessity for a diagnostic classification. This perhaps requires a definition of terms used, in order that there may be no misunderstanding. By peritonitis, we mean an inflammatory reaction of the serous lining of the abdominal cavity either on the parieties or on the contained organs which results in an increase above the normal of the free fluid within the cavity and a loss of the normal smoothness, sheen and color of the membrane itself, with the deposition of fibrin on the surface. This may be a local process with or without an adherence of adjacent surfaces to form a limiting wall. The former we have called acute local peritonitis, the latter an abscess. If the process was not localized and the limits or boundaries were not evident, we have called the process acute diffuse peritonitis. A determination of the focus of the infection has been made without difficulty in all but eight cases. Five of these were abscesses in the right lower quadrant in which the appendix was not seen but was probably the source of the infection. One patient had a pelvic abscess which formed after the incidental removal of an appendix during an operation for another lesion. The cause of one fairly extensive acute diffuse peritonitis, thought at first to be of tuberculous origin, was and is still a mystery. In one case there was a diffuse peritonitis from a questionable perforation of the sigmoid diverticulum or an appendix epiploica. A summary of all the cases, according to these diagnoses, is given in table 1. It is seen that certain diseases frequently associated with peritonitis are absent from our series. This is chiefly because the genito-urinary and gynecologic departments are separate from the main surgical service. This explains the absence of cases due to rupture of the bladder, ureter, kidney or pelvis and the relatively small number of cases with tubal infection. The relatively common children's peritonitis of the pneumonococcus and hemolytic streptococcus variety is likewise absent, possibly because of our rather limited pediatric service, although 12 per cent of our patients were less than 10 years of age. The only fulminating streptococcic case in our series occurred in an adult. Postoperative peritonitis is represented only by the three cases of volvulus. No doubt others occurred during the course of the study which did not come to operation. Thus it will be seen that these figures cannot be taken to show the proportional causes of peritonitis except so far as it is seen in a general surgical service. Under these circumstances, one is not surprised to find that about three fourths of the cases were due to acute appendicitis.

A summary of the clinical features and bacteriologic observations of the whole group simply give a confused mass of statistics which have little meaning. It is only when we divide them according to cer-

tain pathologic diagnoses that the important features of the study can be made plain, and sometimes it is necessary to subdivide still further and even to analyze the individual cases to bring out the most significant points. Although we hesitate to draw general conclusions from small groups of cases, a perusal of table 1 will give some indication of the relationship of certain lesions to the extent of peritoneal involvement; for example, the great majority of cases of acute appendicitis in which the lesions did not perforate or become gangrenous seem to be associated with acute local peritonitis rather than with acute diffuse peritonitis or

TABLE 1.—*Pathologic Diagnosis in One Hundred and Six Cases of Peritonitis*

Acute appendicitis with acute local peritonitis	31		
Acute appendicitis with acute diffuse peritonitis	4	37	
Acute appendicitis with abscess	2		
Perforated appendicitis with acute local peritonitis	2		
Perforated appendicitis with acute diffuse peritonitis	11		
Perforated appendicitis with abscess	12	30	76
Perforated (?) appendicitis with abscess	5		
Gangrenous appendicitis, no perforation but acute local peritonitis	6		
Gangrenous appendicitis, no perforation but acute diffuse peritonitis	2	9	
Gangrenous appendicitis, no perforation but abscess	1		
Volvulus of ileum with acute diffuse peritonitis	2		
Strangulated hernia with acute local peritonitis	2		
Perforated duodenum with acute diffuse peritonitis	2	10	
Perforated jejunum with acute diffuse peritonitis	1		
Perforated ileum with acute diffuse peritonitis	3		
Volvulus of sigmoid with acute diffuse peritonitis	1		
Perforated colon with acute local peritonitis	1		
Perforated colon with acute diffuse peritonitis	3	6	
Perforated (?) colon with acute diffuse peritonitis	1		
Acute cholecystitis with acute local peritonitis	2		
Acute cholecystitis with acute diffuse peritonitis and pancreatitis	1		
Perforated cholecystitis with acute diffuse peritonitis	2	6	
Perforated cholecystitis with abscess	1		
Acute mesenteric lymphadenitis with acute local peritonitis	2		
Puerperal fever with acute diffuse peritonitis	1		
Puerperal fever with abscess	1		
Acute salpingitis with acute local peritonitis	1	8	
"Ideopathic" hemolytic streptococcic acute diffuse peritonitis	1		
"Ideopathic" unknown cause acute diffuse peritonitis	1		
"Ideopathic" unknown cause pelvic abscess	1		

abscess. The great majority of cases of perforated appendicitis seem to be associated with acute diffuse peritonitis or abscess in about equal proportions. Gangrenous appendixes which have not perforated are more likely to be associated with an acute local peritonitis than with an abscess or an acute diffuse peritonitis. Perforated lesions of the intestine seem to be associated with an acute diffuse peritonitis rather than with a localized process.

We shall present the results of our study from four different points of view: the pathologic diagnosis; the extent and nature of peritoneal involvement; the growth of organisms; the untoward results. In the tables, an attempt is made to show the correlation between the clinical course and the factors being considered. Only the more striking features are significant, and too definite conclusions must not be drawn

from small groups of cases. The points which seem to us significant are indicated by an asterisk.

CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE PATHOLOGIC CONDITION

LESIONS OF THE APPENDIX

Acute Appendicitis with Acute Local Peritonitis.—Table 2 summarizes the largest single group, namely, acute appendicitis with acute

TABLE 2.—*Analysis of Acute Appendicitis with Acute Local Peritonitis—Thirty-One Cases*

	Number	Per Cent
Time:		
12 hours	7	23*
24 hours	15	48*
48 hours	6	19*
72 hours	1	3
96 hours	0	0
96+ hours	2	6
Nausea +	24	77
Nausea 0	7	23
Vomiting +	20	67
Vomiting 0	10	33
Chill +	2	14
Chill 0	12	86
Fever +	26	87
Fever 0	4	13
Typical	24	77*
Atypical	7	23*
Diarrhea +	2	8
Diarrhea 0	23	92
Constipation +	7	28
Constipation 0	18	72
Obstipation +	0	0
Obstipation 0	24	100
Quadrant 1	21	68*
Quadrant 2	7	23*
Quadrant 3	1	3
Quadrant 4	2	6
Tenderness +	31	100
Tenderness 0	0	0
Rigidity +	18	62
Rigidity 0	11	38
Rebound tenderness +	15	80
Rebound tenderness 0	5	20
Distention +	0	0
Distention 0	14	100
Mass +	0	0
Mass 0	25	100
Pelvic signs +	19	63
Pelvic signs 0	11	37
White blood cells 16,000 +	21	75*
White blood cells 16,000 —	7	25*
Polymorphonuclears 80% +	21	78*
Polymorphonuclears 80% —	6	22*
Mild	21	68*
Moderate	10	32*
Severe	0	0*
1 to 20 years	15	48
21 to 40 years	10	32
40+ years	6	19
Fluid:		
Little	29	94*
Much	2	6*
Clear	6	19*
Turbid	25	81*
Thick	0	0
Smear (forms seen)		
?	11	..
0	17	85*
1	3	15*
2	0	0
3	0	0
Bacterial Growth:		
0 species	24	77*
1 species	3	10*
2 species	0	0*
3 species	3	10*
4 species	1	3*
5 species	0	0
6 species	0	0
B. coli	5	16*
Green streptococcus	2	6*
C. welchii	2	6*
Sequelae 0	22	71*
1 to 3	9	29*
4 to 7	0	0*
Days 15 —	25	81*
Days 16 +	6	19*
Recovered	31	100*
Died	0	0*

* As stated in the paper, only the striking features are significant; in this and the following tables, those points which seem to us of importance are indicated by an asterisk.

local peritonitis, comprising thirty-one cases. It seems to us that the significant points in this group are: More than two thirds of the patients came to the hospital within the first twenty-four hours and almost all of them within two days. About four-fifths had a typical history, which probably rendered an early diagnosis easy. In two thirds of the cases the signs were limited to one quadrant of the abdomen. Three fourths of the cases showed a total white cell count above 16,000 and polymorphonuclears over 80 per cent, which was the average count for the whole series. These cases averaged 18,000 white blood cells,

with 85 per cent polymorphonuclears. None of the patients seemed to be seriously ill; two-thirds were considered to be mild cases, and only one-third were moderately ill. Two thirds of the patients had no untoward postoperative symptoms, and the other third had relatively few and mild ones. All of the patients recovered, and five sixths of them left the hospital within fifteen days. With regard to the peritoneal fluid, the quantity was relatively small in four fifths of the cases. It was turbid in most, and not thick in any case. It was without odor in all instances. In one third of these cases no smear was made of the peritoneal fluid; of the other two-thirds, 85 per cent showed no organisms and 15 per cent (three cases) showed only a single type. Of these three, one proved to grow a single organism but the other two grew three and four species, respectively. No gram-positive bacilli were seen in the smear, although seven species of these types grew out, which indicates that they were present in relatively few numbers in the peritoneal fluid. The cultures yielded no growth in twenty-four, or 77 per cent, of the cases. Cultures were positive in seven cases, or 23 per cent. The most common species was nonhemolytic *B. coli*, which appeared in five cases, while the green streptococcus, *C. welchii* and aerobic and anaerobic diphtheroids appeared in two cases each. Three of the seven cases yielded a single species on culture. Two of these were *B. coli* and one an anaerobic diphtheroid. In three cases three species were found and in one, four. In the latter case, only one form was seen in the smear, so that the others must have been present in extremely small numbers.

Acute Appendicitis with Acute Diffuse Peritonitis.—There were only four cases in this group, so that any conclusions drawn from them may be misleading. The points wherein they differ from the larger group are, however, suggestive. All of the patients had nausea, vomiting and fever. All had signs in more than one quadrant of the abdomen. All had tenderness and rigidity, while rebound tenderness was noted in three but not mentioned in one. All had a differential polymorphonuclear count of over 85 per cent, although the total count fell below 16,000 in one case. All the patients were more than mildly ill. All recovered, but three had to stay in the hospital more than sixteen days. Bacterial growth was found in the peritoneal exudate in all but one case, but *C. welchii* was not found.

Acute Appendicitis with Localized Abscess.—There were only two cases of acute appendicitis without gangrene or perforation in which a localized abscess had developed. These cases differ from those in the preceding two groups in that in both the symptoms were of more than four days' duration. Both had signs limited to one quadrant. *B. coli* was found in both cases, and the patients required hospitalization for

more than sixteen days. The cases are similar to those in the preceding group in that in both there were nausea, vomiting and fever, the patients were more than mildly sick, and neither group yielded *C. welchii.*

Comment on the Cases of Acute Appendicitis Without Gangrene or Perforation.—The recovery of all of the patients with acute appendicitis accompanied with acute local peritonitis is the most striking feature of table 2. These patients came to the hospital early before the appendix had ruptured or the contained organisms had entered and multiplied in the peritoneal cavity. One would expect to find that these two facts were in some way related to one another. Localization of signs corresponded to localization of infection. Symptoms and signs were of importance only as they pointed to the diagnosis. A high white cell count was usually found. The general aspect of the patients indicated a relatively benign disease. The peritoneal reaction was limited in extent. There was usually not much fluid, but it was turbid, indicating cellular elements. Smears and cultures were generally negative. The turbidity of the fluid does not indicate the presence of bacteria, necessarily. Seven of these cases demonstrate that it is possible for bacteria to penetrate a grossly intact wall of the appendix. *B. coli* apparently is most likely to do this; *C. welchii* and green streptococci may do it. Stout [29] demonstrated that the mucosa is broken in all cases of acute appendicitis. Organisms presumably invade the wall and may move about in the circulating fluid or be carried about by phagocytes. Leukocytes are given off into the peritoneal cavity and may carry with them viable organisms. If they are not destroyed by the phagocyte, they may in turn multiply within it and destroy it and thus be liberated in the peritoneal cavity. *C. welchii* frequently repels leukocytes, and it may be less frequently carried by them through the wall of the intestine. In the four cases of acute appendicitis with acute diffuse peritonitis the process had gone a little farther than in the preceding group, but there had been no localization. Signs were present indicative of wider spread of infection, but still the organisms were not present in very great numbers. The sequelae indicated that the body had more trouble overcoming the infection than it did in the preceding group of cases. In the cases of abscess, the organisms or their products had been carried through the wall or had penetrated to such a degree that a strong exudative reaction had been set up by the peritoneum. There was sufficient time, however, for this defense to establish itself and control the spread of the infection by a plastic process. The organisms were able to gain a foothold and multiply outside of the wall of the appendix. Just what part the resistance of the individual

29. Stout, A. P.: Unpublished work.

and the virulence of the organisms had to play in this and how much it was due to pure chance of anatomic location, it is difficult to say.

Perforated Appendix with Acute Local Peritonitis.—In contradistinction to the group of cases of acute appendicitis in which there was no gangrene and no perforation, the perforated appendixes usually

TABLE 3.—*Analysis of Perforated Appendix with Acute Diffuse Peritonitis—Eleven Cases; Perforated Appendix with Abscess—Twelve Cases*

	Acute Diffuse Peritonitis	Per Cent	Appendix with Abscess	Per Cent
Time				
12 hours	0	0	1	8
24 hours	1	9	0	0
48 hours	4	36*	1	8
72 hours	2	18*	2	17*
96 hours	2	18*	3	25*
96+ hours	2	18*	5	42*
Nausea +	9	90	11	92
Nausea 0	1	10	1	8
Vomiting +	9	82	11	92
Vomiting 0	2	18	1	8
Chill +	3	50	2	33
Chill 0	3	50	4	66
Fever +	11	100	12	100
Fever 0	0	0	0	0
Typical	8	73*	9	75*
Atypical	3	27*	3	25*
Diarrhea +	2	29	0	0
Diarrhea 0	5	71	10	100
Constipation +	4	57	4	33
Constipation 0	3	43	8	67
Obstipation +	1	14	0	0
Obstipation 0	6	86	11	100
Quadrant 1	2	18	6	50
Quadrant 2	0	0	4	33
Quadrant 3	1	9	0	0
Quadrant 4	8	73	2	17
Tenderness +	11	100	12	100
Tenderness 0	0	0	0	0
Rigidity +	10	91	10	91
Rigidity 0	1	9	1	9
Rebound tenderness +	7	88	3	75
Rebound tenderness 0	1	13	1	25
Distention +	4	80	5	63
Distention 0	1	20	3	38
Mass +	1	17	7	70
Mass 0	5	83	3	30
Pelvic +	6	60	3	30
Pelvic 0	4	40	7	70
White blood cells				
16,000 +	3	30*	7	64*
16,000 —	7	70*	4	36*
Polymorphonuclears				
80% +	5	50*	7	70*
80% —	5	50	3	30*
Mild	0	0	1	8
Moderate	6	55*	8	67*
Severe	5	45*	3	25*
1 to 20 years	6	55	3	25
21 to 40 years	1	9	2	17
40+ years	4	36	7	58
Fluid				
Little	2	18	2	17
Much	9	82*	10	83*
Clear	0	0	0	0
Turbid	8	73*	3	25
Thick	3	27	9	75*
Smear (forms)				
?	0	0	1	..
0	0	0	1	9
1	0	0	0	0
2	7	64*	3	27*
3	4	36*	7	64*
Bacteria (growth)				
0 species	0	0*	0	0
1 species	1	9*	0	0
2 species	2	18*	2	17*
3 species	3	27*	4	33*
4 species	4	36*	2	17*
5 species	1	9*	2	17*
6 species	0	0*	2	17*
B. coli	11	100*	12	100*
Green streptococcus	6	55*	9	75*
C. welchii	3	27*	7	58*
Sequelae 0	2	18	4	36
1 to 3	4	36*	6	55*
4 to 7	5	46*	1	9
Days 15—	2	18	2	17
Days 16+	9	82*	10	83*
Recovered	8	73*	10	83*
Died	3	27*	2	17*

resulted in either a well walled-off abscess or an extensive diffuse process. Acute local peritonitis was found in only two cases of this series. These do not differ strikingly from the other two groups of perforated appendixes. It has been impossible in most of the cases of this group to determine from the history just when the perforation took place. It may be that in these two instances it had occurred a relatively short time before operation. One point seems to be of significance in these two cases. Both patients recovered, although both yielded four different species of organisms from the peritoneal exudate, includ-

ing *B. coli.* However, one was in the hospital sixty-one days after operation and had numerous complications. The other had no sequelae and went home on the twenty-first day. The culture from the former yielded *C. welchii* and the hemolytic streptococcus as well as *B. coli;* in the latter case, these other organisms were absent.

Perforated Appendix with Acute Diffuse Peritonitis.—This group contains eleven cases and may be contrasted with the one that follows in which perforation was present with abscess. Table 3 brings out several striking dissimilarities between these two groups, and both of them in turn differ in many respects from the first group which is shown in table 2. It is seen that the majority of the patients came to the hospital after forty-eight hours of symptoms, and only one came in the first twenty-four hours. Still, three fourths of these cases gave a typical history, and the disease should have been diagnosed almost as easily as in the first group. Nausea, vomiting, chill, fever, diarrhea, constipation and obstipation were all more prominent features of the history. Three fourths of the patients gave signs in all four quadrants of the abdomen, while tenderness, rigidity, rebound tenderness and distention were more frequent. On the other hand, the blood counts were much lower as a rule, the total count being below 16,000 in 70 per cent and the polymorphonuclear percentage below 80 per cent in half of the cases. None of the cases was mild, and in half of them the patients were markedly ill at the time of operation. Only two were in the hospital for less than fifteen days, and both of them died. The average period of hospitalization for those who did not die was thirty days. All but two of the patients had postoperative complications. Marked infection of the abdominal wall was the most frequent untoward sequel. Four of the patients had pneumonia. Three of the patients died. The peritoneal exudate was in great quantity in all but two of the cases. No odor was present in four of the cases, while in four others it was foul and in two fecal. No observation with regard to this point was made in one case. All of the smears from the fluid showed at least two forms of bacteria, and four of them showed all three. No cultures were sterile, and seven of the eleven yielded from three to four different species. In every case nonhemolytic *B. coli* was found, and in four the hemolytic variety as well. More than half showed the green streptococcus and one fourth *C. welchii,* while one third of the cases yielded an anaerobic streptococcus. The three fatal cases had these things in common: the patients were over 45 years of age; more than five complications occurred, and a thick fluid was present with a combination of nonhemolytic *B. coli* and the green streptococcus. Only one of the fatal cases yielded *C. welchii.*

Perforated Appendix with Abscess.—The twelve cases in this group are summarized with the preceding group in table 3. They differ from

those in the former group in having a longer history of symptoms, two thirds of them having lasted for more than four days. Nausea, vomiting and fever were prominent features, but diarrhea, constipation or obstipation were not. As in the preceding group, the history was typical in three fourths of the cases. The signs were generally limited to one or two quadrants. As with the cases of diffuse peritonitis, most of the patients with abscess were moderately or markedly ill. The blood counts in general were higher, but the "resistance line" of Gibson [30] indicated an unfavorable prognosis in two thirds of the cases. Two of the patients died, both showing a falling "resistance line." In those who survived, the complications were mild, while in the diffuse cases they were severe. The survivors, as in the preceding group, stayed in the hospital on an average of about a month. The peritoneal exudate was present in considerable quantities and was usually thick. It had a foul odor in three fourths of the cases. In ten of eleven, more than one morphologic form was seen in the smear and in seven, three kinds were present. As in the preceding group, gram-positive bacilli were never seen in the absence of both gram-negative bacilli and gram-positive cocci. All yielded nonhemolytic *B. coli;* the green streptococcus was present in three fourths of the cases and *C. welchii* in half. Again, half of the cases yielded four or more different species, six being found in two cases and five in two. The two fatal cases had in common much fluid with a foul odor yielding *B. coli* and green streptococci. Only one had *C. welchii.* Both were 65 years of age or over.

Localized Abscess in the Right Lower Quadrant with Questionable Perforation of the Appendix.—There were five cases with large abscesses in the right lower quadrant in which the appendix could not be seen and no effort was made to remove it. They were similar in many ways to the preceding group, and might have been classified with them. The exudate in four of these five cases was present in large amount and was thick. The smears showed two or more forms, and the cultures two or more species. Nonhemolytic *B. coli* was present in all of these cases, green streptococcus in two and *C. welchii* in only one which was not fatal.

Comment on Cases of Perforated Appendix.—The majority of the patients in these groups came to the hospital late in spite of the fact that in three fourths of the cases there was a typical history of pain. The question is not yet settled as to the cause of perforation of an appendix. Except for the rare penetration of a foreign body, we must presuppose a death of tissue and a solution of continuity of tissue fibers

30. Gibson, C. L.: The Value of the Differential Leucocyte Count in Acute Surgical Diseases, Ann. Surg. **43**:485, 1906.

either by liquefaction or by rupture from pressure. Clinically, it has been thought possible at times to tell when perforation has taken place either by a sudden relief from pain, due supposedly to the release of distention of the inflamed appendix, or a sudden increase of pain from the irritation of a large area of peritoneal serosa by a quantity of intestinal contents. In both of these instances, there is probably an explosive element to the perforation. In most cases, however, it is not possible to tell when the perforation has taken place, and in these instances the element of force in the rupture is probably minimal. In either case, as the wall breaks or parts, the contents, including bacteria, disintegrating food particles and digestive ferments, escape. The amount depends on the size of the opening and the force behind it. It is of interest that in our group of twenty-five cases of known perforation of the appendix, two were found in an early stage of acute local peritonitis, and the patients recovered. The eleven patients with acute diffuse peritonitis came in late, in spite of the fact that three fourths of them had a typical history. Symptoms and signs were all extensive. The patients were markedly ill; the infection had spread extensively, as indicated by the large quantity of fluid which showed bacteria on smears and yielded positive cultures in every case. In these there was no evidence of the body's ability to localize the infection. The blood count suggests a losing battle against overwhelming odds. It is possible that some of these patients would eventually have overcome the infection without operation, but it is fair to assume that operation with the removal of the distributing focus, thus stopping the outpouring of fecal material, stemmed the tide of spread and gave the body a chance to overcome the infection if it could. This it failed to do in one fourth of the cases. In the twelve cases of abscess we must presuppose either that there was a wall already prepared before the perforation or that the spread of infection was so slow that time was given for the protective mechanism to be built up. In several of these cases, although there was definite abscess formation, there was some degree of diffuse inflammation around the abscess. In a number of cases, when the peritoneal cavity was opened, an excess of peritoneal fluid was found, and later an abscess was located containing exudate of a different character. Smears and cultures of these free fluids usually revealed either no organisms or fewer organisms than the abscess fluid, showing that the general peritoneum was either reacting to diffusible products of the local infection or destroying the organisms that were wandering afield, or else that certain organisms were able to spread abroad against the defense of the peritoneal fluid while others could not. It would seem to be worthy of note that *C. welchii* was found in the peritoneal fluid in only twelve of the thirty cases of perforative appendicitis and in only two of the six fatal cases. This organism is so easily identified

that we feel confident that this figure represents the actual incidence of *C. welchii* in our specimens. Our results seem to indicate either that it is not so frequent as is supposed to be in the ileocecal region, or that it could not maintain itself in the peritoneal cavity. Perhaps the latter condition is not surprising when we know that it grows best on glycogenic tissues. In this group of cases it does not seem to have been a very potent factor in the mortality, and it may be that in association with other organisms it cannot produce its potent toxin. It is true that certain organisms will prevent the formation of toxin when growing with *C. welchii* in vitro. It would seem to be fair to assume that if a perforation of the intestine takes place, a larger mass of organisms enters the peritoneal cavity through this gross aperture than would ordinarily come through an intact wall. In the cases with perforation, therefore, we have to deal with a relatively large initial bacterial dosage, which cannot be measured, and a certain amount of intestinal juice containing more or less active digestive ferments and also foreign bodies in the form of partially digested or indigestible food. What part the latter substances play in the development of peritonitis it is difficult to say, but from what we know of the irritating character of these substances, they may be of considerable importance. This is a question warranting further investigation.

Gangrenous Appendicitis Without Perforation with Acute Local Peritonitis.—There were six cases in which the appendix was gangrenous either as a whole or in part, without any gross evidence of perforation, but was surrounded by a local uncircumscribed area of peritonitis (table 4). All but one of these patients came to the hospital within forty-eight hours of the onset of symptoms. All but one gave a typical history. All were either mildly or moderately ill. In four, the signs were limited to one quadrant. The sequelae were mild, and all the patients recovered. The peritoneal fluid was turbid in all cases but without odor. The smear showed no organisms in two, but was positive in three. Only one showed no growth; four of the others showed two or more bacteria. The nonhemolytic *B. coli* was present in only one-half of the cases; the green streptococcus was present in only one case. *C. welchii* was not found at all.

Gangrenous Appendicitis Without Perforation with Acute Diffuse Peritonitis.—There were only two cases in this group. They differ from those in the preceding group in the greater severity of symptoms and the greater extent of the signs, but recovery resulted in both with only mild sequelae. There was much peritoneal exudate, but it had no odor. In one fluid no organisms were seen on smear, but four different species grew out of both fluids. Nonhemolytic *B. coli* was present in both cases, but the green streptococcus in only one and *C. welchii* in neither.

Gangrenous Appendicitis Without Perforation with Localized Abscess.—Only one case in the series fell into this group. A definitely localized abscess was found in this case. The lesion differed from that in the cases in the preceding group chiefly in its localization. The patient recovered with mild sequelae. The smear showed gram-positive cocci as well as gram-negative bacilli, but only the latter appeared in the culture.

TABLE 4.—*Analysis of Gangrenous Appendix Without Perforation with Acute Peritonitis—Six Cases; with Acute Diffuse Peritonitis—Two Cases*

	Acute Local Peritonitis	Per Cent	Acute Diffuse Peritonitis	Per Cent
Time				
12 hours	1	17*	0	0
24 hours	2	33*	1	50
48 hours	2	33*	1	50
72 hours	1	17*	0	0
96 hours	0	0	0	0
96+ hours	0	0	0	0
Nausea +	5	83	2	100
Nausea 0	1	17	0	0
Vomiting +	3	50	2	100
Vomiting 0	3	50	0	0
Chill +	1	33	0	0
Chill 0	2	67	0	0
Fever +	5	83	2	100
Fever 0	1	17	0	0
Typical	5	83	1	50
Atypical	1	17	1	50
Diarrhea +	0	0	0	0
Diarrhea 0	4	100	2	100
Constipation +	2	50	1	50
Constipation 0	2	50	1	50
Obstipation +	0	0	0	0
Obstipation 0	4	100	2	100
Quadrant 1	4	67	0	0
Quadrant 2	1	17	1	50
Quadrant 3	1	17	0	0
Quadrant 4	0	0	1	50
Tenderness +	6	100	2	100
Tenderness 0	0	0	0	0
Rigidity +	5	83	2	100
Rigidity 0	1	17	0	0
Rebound tenderness +	5	100	2	100
Rebound tenderness 0	0	0	0	0
Distention +	1	17	2	100
Distention 0	5	83	0	0
Mass +	0	0	0	0
Mass 0	5	100	2	100
Pelvic sign +	3	60	1	50
Pelvic sign 0	2	40	1	50
White blood cells				
16,000 +	4	67	1	50
16,000 —	2	33	1	50
Polymorphonuclears				
80% +	5	83	1	50
80% —	1	17	1	50
Mild	2	33*	0	0*
Moderate	4	67*	2	100*
Severe	0	0	0	0
1 to 20 years	0	0	0	0
21 to 40 years	4	67	2	100
40+ years	2	33	0	0
Fluid				
Little	4	67	0	0
Much	2	33	2	100
Clear	0	0	0	0
Turbid	6	100	2	100
Thick	0	0	0	0
Smear (forms)				
?	1	..	0	..
0	2	40*	1	50
1	1	20*	0	0
2	2	40*	0	0
3	0	0	1	50
Bacteria (growth)				
0 species	1	17*	0	0
1 species	1	17*	0	0
2 species	3	50*	0	0
3 species	0	0	0	0
4 species	0	0	2	100*
5 species	1	17*	0	0
6 species	0	0	0	0
B. coli	3	50*	2	100*
Green streptococcus	1	17*	1	50*
C. welchii	0	0*	0	0*
Sequelae 0	2	33*	1	50*
1 to 3 days	4	67*	1	50*
4 to 7 days	0	0	0	0
Days 15—	2	33*	0	0
Days 16+	4	67*	2	100*
Recovered	6	100*	2	100*
Died	0	0	0	0

Comment on Gangrenous Appendix Without Perforation.—Our observations in these nine cases are surprising in two respects. First, the great majority of them resulted merely in a local peritonitis, one as an abscess and the other six as simple acute local peritonitis. It is quite possible that perforation would have occurred in all of these cases, but operation was performed in the preperforative stage before organisms had invaded the peritoneal cavity in very great numbers. Secondly, although other intestinal organisms were found in culture, *C. welchii*

was not recovered from a single case in the group. This would lead us to believe that, contrary to the opinion of Weinberg and others, this organism is usually not particularly active in the gangrene of appendicitis, and this is further confirmation of our observations in the cases with perforation. One may ask, "What about the other anaerobes?" If we include our cases of perforative appendicitis with our gangrenous group, as we think we may fairly do, we find that in our series there were thirty-nine definitely gangrenous lesions of the appendix and thirty-seven definitely nongangrenous lesions. Twenty-eight different species were found in the nongangrenous cases and one hundred and twenty-four in the gangrenous cases, but if we study the proportion of aerobes to anaerobes in these two groups, we find that in the nongangrenous cases the aerobes represented 75 per cent and the anaerobes 25 per cent, while in the gangrenous cases the aerobes comprised 72 per cent and the anaerobes 28 per cent. We can only say, for our series at least, that in the gangrenous cases we were not able to cultivate anaerobes from the peritoneal fluid in any greater proportion relative to the aerobes than in the nongangrenous cases. Whether they were more numerous within the lumen of the appendix as Weinberg has stated, we are not able to judge. Perforative lesions were found in almost all of Heyde and Runeberg's cases, and these showed many gram-negative anaerobes. The cause of gangrene of the appendix or the intestine has been the subject of much speculation and discussion in the literature on peritonitis. In general, two factors have been considered, the interference of blood supply and the direct action of bacteria. We know that in other parts of the body the simple cutting off of the blood supply results in local death, as for example, in popliteal aneurysm or arteriosclerotic gangrene of the foot. In the intestine or appendix it is impossible to have a sterile gangrene, but the cutting off of the blood supply by strangulation or by edema or by local thrombosis almost certainly plays a part. We do not agree with Corner,[31] who makes the element of time the criterion of whether or not the gangrene of strangulated hernia is due to bacterial action or due to the cutting off of the blood supply. He believed that gangrene developing within twenty-four hours was due primarily to bacterial action. It is obvious that there are usually different mechanical factors operating to make the cutting off of blood supply of an appendix different from that of the intestine. In the former, the small size of the lumen increases the element of pressure from within when edema of the wall or impaction of fecaliths takes place. In the latter, except in the cases of mesenteric thrombosis or an impacted gallstone, the pressure on blood vessels is usually exerted from without. Kelly[18]

31. Corner, E. M.: Acute Infective Gangrenous Processes (Necroses) of the Alimentary Tract, Erasmus Wilson Lecture, Lancet **1**:1410, 1904.

presented as a rarity a case in which there seemed to be gangrene of the mucous membrane of an appendix without edema of the rest of the wall, and this he thought to be due to bacterial action rather than to occlusion of a blood vessel. We know of certain conditions, such as hemolytic streptococcus gangrene [32] or gangrene of the abdominal wall,[33] due apparently to the symbiosis of intestinal organisms, in which bacterial activity seemed to be the primary factor, but even with these it is not clear whether it is the result of the direct action of bacterial products on the tissues or the secondary result of thrombosis of blood vessels or their occlusion by edema. Are there bacteria within the intestine that can of themselves or in combination with other organisms, aerobic or anaerobic, so injure mucous membrane that they may invade the tissues, or must the primary insult be due to a mechanical injury? Heyde [22] and others expressed the belief that while some bacteria may be able to act directly, others that enter the tissues at a point of injury adapt themselves to the body fluids, increase in virulence, become pathogenic, and then proceed to act directly on the tissue. While we do not question the possibility of this, particularly when more than one species is present, we believe that in the case of the appendix the factor of the occlusion of the blood vessel is of prime importance before liquefaction and perforation can take place. We have frequently seen thrombosed vessels near local areas of gangrene or thrombosis of mesenteric vessels when extensive gangrene of the appendix has taken place. Of particular interest and importance is the fact that in many gangrenous appendixes the gangrene extends down to within 1 cm. of the cecum and then stops, fortunately for the surgeon, leaving enough relatively normal wall for inverting the stump. This portion of the appendix is not easily occluded, and it may derive its blood supply from the cecal wall or from the artery that comes up through the wall and makes its exit into the mesentery about 1 cm. from the cecum. This would seem to lend weight to the idea that gangrene of the intestine does not usually take place by the action of bacteria where it is difficult to interfere with the blood supply of the part.

LESIONS OF THE SMALL INTESTINE

Ten of the cases fall under this heading. They are analyzed in table 5. For purposes of comparison, they may be divided into two groups, those in which the lesions were perforative and those in which

32. Meleney, F. L.: Hemolytic Streptococcus Gangrene, Arch. Surg. **9**:317, (Sept.) 1924.

33. Brewer, G. E., and Meleney, F. L.: Progressive Gangrenous Infection of the Skin and Subcutaneous Tissues, Following Operation for Acute Perforative Appendicitis; A Study in Symbiosis, Ann. Surg. **84**:438, 1926.

they were obstructive. The latter group consists of two cases of strangulated hernia and two cases of volvulus.

Perforative Lesions of the Small Intestine.—Fever was a prominent feature. Constipation, obstipation and distention were of no particular importance. The total blood count was low, and the number of polymorphonuclears proportionally high. On the patient's admission to

TABLE 5.—*Analysis of Lesions of the Small Intestine, Perforative—Six Cases; Nonperforative—Four Cases*

	Perforative	Per Cent	Nonperforative	Per Cent
Time				
12 hours	3	50*	0	0
24 hours	2	33*	2	50*
48 hours	0	0	1	25*
72 hours	0	0	0	0*
96 hours	0	0	1	25*
96+ hours	1	17	0	0
Nausea +	4	80	4	100
Nausea 0	1	20	0	0
Vomiting +	4	80	4	100
Vomiting 0	1	20	0	0
Chill +	0	0	0	0
Chill 0	3	100	1	100
Fever +	5	83	2	50
Fever 0	1	17	2	50
Diarrhea +	0	0	1	33
Diarrhea 0	6	100	2	67
Constipation +	2	33	4	100
Constipation 0	4	67	0	0
Obstipation +	0	0	3	100*
Obstipation 0	6	100*	0	0
Quadrant 1	1	17*	2	50*
Quadrant 2	1	17*	0	0*
Quadrant 3	1	17*	0	0*
Quadrant 4	3	50*	2	50*
Tenderness +	5	100	4	100
Tenderness 0	0	0	0	0
Rigidity +	6	100	0	0
Rigidity 0	0	0	2	100
Rebound tenderness +	1	100	0	0
Rebound tenderness 0	0	0	2	100
Distention +	1	17*	4	100*
Distention 0	5	83*	0	0*
Mass +	0	0	2	67
Mass 0	5	100	1	33
Pelvic signs +	2	40	0	0
Pelvic signs 0	3	60*	1	100*
White blood cells				
16,000 +	1	20*	1	50*
16,000 —	4	80*	1	50*
Polymorphonuclears				
80% +	3	60*	2	100*
80% —	2	40*	0	0
Mild	0	0	0	0
Moderate	4	67*	2	50*
Severe	2	33*	2	50*
1 to 20 years	0	0	0	0
21 to 40 years	2	33*	2	50*
40+ years	4	67*	2	50*
Fluid				
Little	2	33	2	50
Much	4	67*	2	50
Clear	0	0	0	0
Turbid	5	83*	3	75*
Thick	1	17*	1	25*
Smear (forms)				
?	1	..	1	..
0	3	60*	2	67*
1	0	0*	0	0*
2	1	20*	0	0*
3	1	20*	1	33*
Bacteria (growth)				
0 species	1	17*	0	0
1 species	0	0*	1	25*
2 species	1	17*	1	25*
3 species	1	17*	0	0*
4 species	1	17*	2	50*
5 species	1	17*	0	0
6 species	1	17*	0	0
B. coli	3	50*	4	100*
Green streptococcus	4	67*	0	0*
C. welchii	3	50*	2	50*
Sequelae 0	1	20	0	0
1 to 3	2	40*	3	75*
4 to 7	2	40*	1	25
Days 15—	3	50	0	0
Days 16+	3	50	4	100
Recovered	2	33	3	75*
Died	4	67*	1	25

the hospital the severity of the condition in the cases with perforation seemed to be about the same as in the cases with obstruction, but the complications were more severe, and four of the six cases were fatal. In three cases, the peritoneal exudate showed nothing in the smear. In one of these in which a lesion of the upper part of the jejunum had become sealed off, no growth was found. In another the fluid specimen came from a patient with a perforated duodenal ulcer. A nonhemolytic and also a green streptococcus were cultivated. The exudate from another case of perforated duodenum showed nothing on smear, but

yielded four different species on culture. This case and the other three in which the ileum had perforated, with from three to five different species of bacteria cultivated from the peritoneal fluid, were fatal. The other two patients recovered.

Nonperforative Lesions of the Small Intestine.—This group of four cases includes two cases of strangulated hernia with gangrene of the intestine that required resection and two cases of postoperative volvulus. These cases differed from those in the preceding group in that fever was not a prominent symptom, while constipation, obstipation and distention were marked. The severity of the cases before operation was judged to be as great as in the cases with perforation, and yet only one of the patients died and the others recovered without serious complication. The fatal case was one in which the volvulus was not relieved at operation, and we feel that this rather than the peritonitis was the chief factor in the fatal outcome. In the two cases of strangulated hernia the intestine was gangrenous without gross perforation. From each of these, four species of bacteria were recovered. *B. coli* and *C. welchii* were present in both, but the green streptococcus was absent. Both patients recovered.

Comment on the Lesions of the Small Intestine.—The most striking feature in this group is that in the cases with and without perforation the patients' condition seemed to be about equally severe on admission to the hospital, but that after operation four of the six patients with perforative lesions died, and only one with obstruction succumbed. In the former group, there was distention in only one case while in the latter group it occurred in all of them. It is obvious that the cause of the clinical severity in these two groups is different. In the group with perforation it is probably due primarily to the bacterial or chemical action within the peritoneal cavity. In the latter, it is manifestly due to the obstruction of the intestine. Relief could not be obtained in the former, so that the three patients with ileal perforations and the one with duodenal perforation of long standing died; in the other cases, obstruction could be and was relieved, except in one case in which the cause of the obstruction was not found and a simple short circuiting operation was not sufficient. The patient in this case died on account of the obstruction rather than on account of the peritonitis, as autopsy showed, even though hemolytic streptococci and *B. coli* were recovered from the peritoneal exudate. In the group of cases with perforation the only two patients to recover were those with duodenal and jejunal perforations in whom bacterial contamination of the peritoneal cavity was minimal. When the perforation was closed, there was no further increase of the irritating factor. The bacterial cultures in this series were interesting. *B. coli* was found in all three and *C. welchii* in two of the cases of obstruction in which

the patients survived. We may assume that because there was no perforation, the bacterial dosage was small and there was no intestinal fluid except that which may have seeped through the wall. *B. coli*, *C. welchii* and the green streptococcus were all present in three of the four fatal cases with perforation. Because of the perforation we may assume that the dosage of bacteria was greater than in the group without perforation, but we cannot overlook the fact that the intestinal

TABLE 6.—*Analysis of the Lesions of the Large Intestines, Perforative—Five Cases; Nonperforative—One Case*

	Number	Per Cent
Time		
12 hours	1	17*
24 hours	2	33*
48 hours	1	17*
72 hours	0	0*
96 hours	1	17*
96+ hours	1	17*
Nausea +	4	67
Nausea 0	2	33
Vomiting +	4	67
Vomiting 0	2	33
Chill +	5	83
Chill 0	1	17
Fever +	5	100
Fever 0	0	0
Diarrhea +	2	33
Diarrhea 0	4	67
Constipation +	5	83
Constipation 0	1	17
Obstipation +	3	50
Obstipation 0	3	50
Quadrant 1	0	0
Quadrant 2	1	17*
Quadrant 3	1	17*
Quadrant 4	4	67*
Tenderness +	6	100
Tenderness 0	0	0
Rigidity +	6	100
Rigidity 0	0	0
Rebound tenderness +	2	67
Rebound tenderness 0	1	33
Distention +	5	100
Distention 0	0	0
Mass +	1	20
Mass 0	4	80
Pelvic signs +	3	50
Pelvic signs 0	3	50
White blood cells 16,000+	3	50*
White blood cells 16,000—	3	50*

	Number	Per Cent
Polymorphonuclears		
80% +	3	60*
80% —	2	40*
Mild	0	0
Moderate	3	50*
Severe	3	50*
1 to 20 years	0	0
21 to 40 years	1	17
40+ years	5	83*
Fluid		
Little	1	17
Much	5	83*
Clear	0	0
Turbid	5	83
Thick	1	17
Smear (forms seen)		
?	1	..
0	1	20
1	1	20
2	2	40
3	1	20
Bacterial growth		
0 species	1	17
1 species	0	0
2 species	0	0
3 species	1	17*
4 species	2	33*
5 species	2	33*
6 species	0	0
B. coli	5	83*
Green streptococcus	3	50*
C. welchii	5	83*
Sequelae ?	1	..
0	1	20
1 to 3	2	40
4 to 7	2	40
Days 15—	1	17
Days 16+	5	83*
Recovered	5	83*
Died	1	17

juices and food particles were also present to a variable degree. It is difficult to say whether the fatal outcome in these cases was due to the bacterial dosage or to the added effect of the intestinal contents.

LESIONS OF THE LARGE INTESTINE

Perforative Lesions of the Large Intestine.—There were five of these cases in the series, four of them with acute diffuse, and one with acute local, peritonitis (table 6). Three of the five patients came to the hospital within twenty-four hours. Constipation was a frequent symptom, with obstipation in two cases. Four of the five patients had signs in all four quadrants, and in all, the abdomen was

distended. None had mild cases; the majority were severely ill. In one case there were no sequelae; in three, the complications were severe. One patient died soon after operation before there was time for complications; the rest recovered. There was considerable turbid fluid in all but one case; in three, the odor was fecal, but in two the fluid was described as having no odor. The four smears which were examined showed organisms, and all of the cultures yielded three or more different species. Nonhemolytic *B. coli* and hemolytic *C. welchii* were present in every case, while the green streptococcus appeared in three.

Nonperforative Lesion of the Large Intestine.—There was only one case in this series, and it is of interest only so far as it differs from the cases in the group with perforation. It was a case of volvulus of the sigmoid of moderate severity, with three quadrants involved. There was much turbid fluid without odor. No organisms were seen in the smear, and the culture yielded no growth. The patient recovered with only one mild sequel.

Comment on Lesions of the Large Intestine.—The cases of perforative lesion of the large intestine are perhaps surprising in two respects, one being that only one of the five patients died, although all of the patients were quite ill on admission. The patient who died came to the hospital almost moribund and died directly after operation. Nevertheless, *C. welchii* were found in all five patients, and all were over 40 years of age. This mortality figure differs strikingly from that in the group of cases of perforative lesions of the small intestine. Tavel and Lanz [10] made the same observation and offered as an explanation the facts that the contents of the small intestine are more fluid and more likely to be spread around after discharge into the peritoneal cavity, because of both the consistency and the greater movement of the intestines. On the other hand, the contents of the large intestine are more solid and the intestine is less freely movable, so that there is less extensive spread. These seem to be logical explanations, but we should like to emphasize two other factors: the irritating effect of the digestive fluids of the small intestine and the greater viability of the bacteria in the small intestine. The absence of lethal activity on the part of *C. welchii* is consistent with our foregoing observations with respect to the perforative and gangrenous appendixes and the lesions of the small intestine.

LESIONS OF THE GALLBLADDER

Acute Cholecystitis with Peritonitis.—There were six cases in this series (table 7). In three, the gallbladder had perforated; in two, there was acute diffuse peritonitis, and in the other a well localized abscess had formed. In two of the three cases without perforation,

acute local peritonitis occurred and acute diffuse peritonitis with acute pancreatitis in one. Most of the patients came to the hospital early because of the severity of their symptoms. All had nausea, vomiting and fever without chills. In the cases with perforation three or four quadrants were involved, while in the others the signs were limited to one or two quadrants. Distention was a prominent feature. Only one

TABLE 7.—*Analysis of Acute Cholecystitis—Six Cases; Perforated—Three Cases, Nonperforated—Two Cases; Nonperforated with Acute Pancreatitis—One Case*

	Perforative	Per Cent	Nonperforate	Per Cent
Time				
12 hours	0	0	0	0
24 hours	1	33	0	0
48 hours	1	33	2	67
72 hours	0	0	0	0
96 hours	1	33	0	0
96+ hours	0	0	1	33
Nausea +	3	100	3	100
Nausea 0	0	0	0	0
Vomiting +	3	100	3	100
Vomiting 0	0	0	0	0
Chill +	0	0	0	0
Chill 0	3	100*	3	100*
Fever +	3	100	3	100
Fever 0	0	0	0	0
Diarrhea +	0	0	0	0
Diarrhea 0	0	0	2	100
Constipation +	1	100	0	0
Constipation 0	0	0	2	100
Obstipation +	0	0	0	0
Obstipation 0	1	100	2	100
Quadrant 1	0	0	1	33*
Quadrant 2	0	0	2	67*
Quadrant 3	2	67*	0	0
Quadrant 4	1	33*	0	0
Tenderness +	3	100	3	100
Tenderness 0	0	0	0	0
Rigidity +	3	100	3	100
Rigidity 0	0	0	0	0
Rebound tenderness +	1	100	1	50
Rebound tenderness 0	0	0	1	50
Distention +	3	100	0	0
Distention 0	0	0	1	100
Mass +	1	33	0	0
Mass 0	2	67	3	100
Pelvic signs +	1	33	0	0
Pelvic signs 0	2	67	2	100
White blood cells				
16,000 +	2	67*	3	100*
16,000 —	1	33	0	0
Polymorphonuclears				
80% +	2	67*	1	33
80% —	1	33	2	67*
Mild	0	0	1	33
Moderate	2	67	1	33
Severe	1	33	1	33
1 to 20 years	0	0	0	0
21 to 40 years	0	0	2	67*
40+ years	3	100*	1	33
Fluid				
Little	1	33	0	0
Much	2	67	3	100
Clear	0	0	0	0
Turb'd	2	67	3	100
Thick	1	33	0	0
Smear (forms)				
?	2	..	0	..
0	1	100	3	100
1	0	0	0	0
Bacteria (growth)				
0 species	0	0	3	100*
1 species	0	0	0	0
2 species	2	67*	0	0
3 species	1	33*	0	0
4 species	0	0	0	0
5 species	0	0	0	0
6 species	0	0	0	0
B. coli	3	100*	0	0
Green streptococcus	2	67*	0	0
C. welchii	1	33*	0	0
Sequelae 0	0	0	2	67*
1 to 3	0	0	1	33*
4 to 7	3	100*	0	0
Recovered	0	0	3	100*
Died	3	100*	0	0

patient was mildly ill. The three patients without perforative lesions recovered without important sequelae. In all of these, the smear showed no organisms, and the cultures yielded no growth. All three of the patients with perforative lesions died with four or five complications, and all showed two or more organisms. *B. coli* was present in all three cases, with the green streptococcus in two and the nonhemolytic streptococcus in one. *C. welchii* was present with *B. coli* and the green streptococcus in one case.

Comment on Lesions of the Gallbladder.—Here the difference between the perforative and nonperforative lesions is striking. The leakage of bile into the peritoneal cavity is not without danger even if it is sterile, and in large amounts it may result in death. This has been demonstrated in laboratory animals by Horrall [34] and others. Small doses of nonpathogenic organisms may prove lethal if small quantities of bile are present. Likewise, it has been demonstrated that sterile bile in the peritoneum may produce a chemical peritonitis of such a degree that bacteria will pass through the wall of an intact intestine in experimental animals. One of these cases seems to illustrate this fact. Cholecystostomy was done, and the bile was reported to be sterile. Some of it leaked into the abdominal cavity and caused peritonitis. The peritoneal exudate at the time of the second operation yielded three different species of intestinal bacteria.

MISCELLANEOUS CASES

In the miscellaneous group, the individual cases of particular interest were (1) the case of fulminating hemolytic streptococcic idiopathic peritonitis starting with a sore throat and (2) the cases of late puerperal fever. The blood culture in the former was sterile, and it is a question whether the spread to the peritoneum was via the intestine or via the retroperitoneal lymphatics. Either of these routes seems more logical than the hematogenous route usually considered for these cases. The case of low grade puerperal fever illustrates a point with regard to anaerobes. The disease had lasted over a month, and the hemolytic streptococcus was presumably of low grade virulence. When first recovered from the peritoneal fluid, it would not grow aerobically on the blood agar plates. It was only after several transplants in meat medium that it would grow aerobically. This evidently illustrates a law that streptococci which have grown for some time in environment without air come to prefer an anaerobic environment. This is seen frequently in abscesses of the brain or lungs and is probably true of many of the intestinal streptococci and possibly of other organisms as well.

A CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE NATURE AND EXTENT OF THE PERITONEAL INVOLVEMENT

ACUTE LOCAL PERITONITIS

There are forty-seven cases in this group, 83 per cent of which were due to appendicitis. The cases are summarized with the other groups

34. Horrall, O. H.: Experimental Bile Peritonitis: Its Treatment in the Dog, Arch. Int. Med. **43**:114 (Jan.) 1929.

in table 8. We wish to call particular attention to the following facts: More than three fourths of the patients came to the hospital within forty-eight hours, and of the appendicitis group, two thirds came in within twenty-four hours. Over three fourths of the patients with appendicitis gave a typical history of that disorder, which is taken to be a generalized abdominal or epigastric pain gradually localizing in the right lower quadrant. Signs were usually present in only one quadrant. The blood count ranged high. None of the patients with appendicitis and only one of the others appeared seriously ill, and complications were mild. Two thirds of the patients had no sequelae. All of them recovered. Almost two thirds of this group went home within fifteen days. The peritoneal exudate was generally not profuse. It was usually turbid but without odor. In one third of the cases no smear of the fluid was made; of the others almost three fourths showed no organisms. In two thirds of the cases the peritoneal fluid yielded no growth in culture, but in one third organisms were present, six of them containing four different species and one containing five. In the seventeen cases of this series showing organisms, nonhemolytic *B. coli* was the commonest species found, being present in thirteen; *C. welchii* was next with seven cases, and the green streptococcus was present in five.

ACUTE DIFFUSE PERITONITIS

This group contains thirty-six cases and differs strikingly from the preceding and succeeding groups in many respects (table 8). The patients did not come to the hospital so early, although the symptoms of nausea, vomiting, chills and fever were more severe. Two thirds of the patients with appendicitis in this group gave a typical history of pain. This does not correspond exactly to the patients who came to the hospital early. In sharp contradistinction to the other groups, over three fifths of these patients had abdominal signs in all four quadrants. The total white blood count was frequently low in this group, but the polymorphonuclear count was high. None of these cases was considered mild. Three fifths of them were considered moderately severe and two fifths were markedly severe. All but one fourth of the patients had postoperative complications, some as many as seven. A third of the patients died, and practically all of the others had a long stay in the hospital. In a great majority of the cases there was a large quantity of peritoneal exudate, either turbid or thick, although in two thirds of the cases it was without odor. Smears of the peritoneal fluid were made in thirty-one cases. No organisms were seen in 29 per cent, while one or more forms were visible in 71 per cent. In five of these cases the fluids yielded no growth, but in the others it yielded one or more species. In one case there were no less than six different species. Nonhemolytic *B. coli* was present in twenty-nine, or 94 per

cent, of the thirty-one fluids yielding growth. The green streptococcus was second with 58 per cent, both of these being more common in the cases of appendicitis than in the other cases. *C. welchii* was third with 39 per cent, but was much more common in the other cases than in the appendicitis group. A nonhemolytic streptococcus was also present in more than one fourth of these cases.

TABLE 8.—*Analysis According to Extent of Peritoneal Involvement—One Hundred and Six Cases*

	Acute Local Perito-nitis		Acute Diffuse Perito-nitis		Abscess	
	No.	%	No.	%	No.	%
Appendicitis	39	85*	17	47*	20	87*
Other	8	17*	19	53*	3	13*
Total	47	..	36	..	23	..
Time						
12 hours	8	17*	4	11*	1	4
24 hours	17	36*	12	33*	0	0
48 hours	12	24*	6	17*	2	13
72 hours	4	8	4	11*	3	13*
96 hours	2	4	3	8*	4	17*
96+ hours	3	6	7	19*	13	56*
Nausea +	37	77	29	88	20	87
Nausea 0	10	23	4	12	3	13
Vomiting +	30	67	29	85	20	87
Vomiting 0	15	33	5	15	3	13
Chill +	3	16	6	32	5	38
Chill 0	16	84	13	68	8	62
Fever +	38	81	34	94	23	100
Fever 0	8	19	2	6	0	0
Typical	30	77*	11	65*	13	65*
Atypical	9	23*	6	35*	7	35*
Diarrhea +	4	11	6	21	0	0
Diarrhea 0	32	89	22	79	18	100
Constipation +	14	40	15	50	7	37
Constipation 0	23	60	15	50	12	63
Obstipation +	3	9	4	13	0	0
Obstipation 0	31	91	26	87	19	100
Quadrant 1	30	64*	4	11	14	61*
Quadrant 2	13	28	5	14	6	26
Quadrant 3	2	4	5	14	1	4
Quadrant 4	2	4	22	61*	2	9
Tenderness +	47	100	35	100	23	100
Tenderness 0	0	0	0	0	0	0
Rigidity +	29	64	32	97	14	78
Rigidity 0	16	36	1	3	4	22
Rebound tenderness +	25	76	16	83	5	55
Rebound tenderness 0	8	24	3	16	4	45
Distention +	5	19	18	72	8	54
Distention 0	21	81	7	28	7	46
Mass +	3	8	3	12	16	76
Mass 0	35	92	23	88	5	24
Pelvic +	24	59	17	55	13	62
Pelvic 0	17	41	14	45	8	38
White blood cells						
16,000 +	27	64*	18	55*	12	60*
16,000 —	15	36*	15	45*	8	40*
Polymorphonuclears						
80% +	29	72*	22	85*	11	58*
80% —	11	28*	4	15*	8	42*
Mild	26	55*	0	0	6	26
Moderate	20	43	21	59*	14	61*
Severe	1	2	15	41*	3	13
1 to 20 years	18	38*	9	25	7	30
21 to 40 years	19	41*	9	25	5	22
40+ years	10	21	18	50*	11	48*
Fluid						
Little	38	81*	9	25	4	17
Much	9	19	27	75*	19	83*
Clear	9	19*	0	0	0	0
Turbid	36	77*	28	78*	6	26
Thick	2	4	8	22*	17	74*
Smear (forms)						
?	15	..	5	..	3	..
0	23	72*	9	29*	2	10
1	5	16*	6	19*	0	0
2	3	9	9	29*	9	45*
3	1	3	7	23*	9	45*
Bacteria (growth)						
0 species	30	64*	5	14*	0	0
1 species	4	9	5	14*	2	9
2 species	3	6	5	14*	6	26*
3 species	3	6	6	17*	6	26*
4 species	6	13	10	28*	3	13*
5 species	1	2	4	11*	4	17*
6 species	0	0	1	3*	2	9
B. coli	13	28*	27	75*	22	96*
Green streptococcus	5	11*	15	42*	15	65*
C. welchii	6	13*	11	31*	10	44*
Sequelae 0	28	60*	8	24	11	48*
1 to 3	18	38*	14	42*	8	35*
4 to 7	1	2	12	36*	3	13
Days 15—	29	62*	9	25	3	13
Days 16+	18	38	27	75*	20	87*
Recovered	47	100*	24	67	19	83
Died	0	0	12	33*	4	17*

PERITONEAL ABSCESS

This group, which is composed of twenty-three cases, has several striking features of its own (table 8). The first is the duration of symptoms before hospitalization, more than one half of the cases appearing after four days. Chill was present in more than one third of the cases in which this symptom was noted. The percentage of cases with a typical history was almost exactly the same as in the cases of diffuse peritonitis. As with the first group, the large majority of cases had

signs limited to one or two quadrants. One fourth of the cases in this group were considered to be mild, one eighth severe, while three fifths fell into the intermediate group. Half of the patients had no sequelae, but some of the rest had as many as four different complications, and four of them died. All who survived were in the hospital a long time. The peritoneal fluid was generally present in considerable quantity and was thick. In over 80 per cent, it had a foul or fecal odor. In three cases a smear was not made; of the other twenty, two showed no organisms, but in all of the others, 90 per cent, more than one form was seen in the smear. Every one of these fluids yielded bacterial growth and only two contained a single species, both of these being from cases of appendicitis. The others all showed multiple species, two of them as many as six different kinds. As with the other two groups, the nonhemolytic *B. coli* takes first place, being present in every case but one. The green streptococcus was present in two thirds of the cases and the hemolytic *C. welchii* in almost 40 per cent.

Comment on the Data from the Standpoint of the Extent of Peritoneal Involvement.—There seems to be a definite relationship between the duration of symptoms before admission and the extent and nature of the peritoneal involvement. The fact that there was a higher percentage of typical histories may have been a factor in bringing the patients in the group with acute local peritonitis to the hospital earlier than the others, but earlier arrival did not correspond with the typical history, and in order that we may have an adequate answer to the question of why patients do not come to the hospital earlier we must go deeper into human reactions to the idea of hospitalization, the reactions of both the family physician and the patient. The earlier age incidence in the first group may explain to a certain degree the early admission to the hospital, or it may indicate the reason for a greater degree of resistance against the infection on the part of the patient. The quadrant signs and the severity of the symptoms, the sequelae and the mortality all correspond to the extent of the inflammation and are to be expected. On the other hand, the turbidity of the peritoneal fluid, the number of organisms seen in the smear and the number of species recovered are greater in the cases of abscess than in the cases of acute diffuse peritonitis, and the three common organisms, *B. coli,* green streptococcus and *C. welchii,* increase in frequency as one passes from the acute local to the acute diffuse and then to the abscess group. The relation of the incidence to the mortality in these three groups is shown graphically in chart 1. Here, of course, other factors offset the factor of bacterial numbers, namely, the limitation of the area of absorption, the limitation of the effective range of activity of the bacteria and the minimal interference to the function of the intestine, all of which render the cases of abscess more benign.

CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE ORGANISMS SEEN IN OR CULTIVATED FROM THE PERITONEAL EXUDATE

STAINED SMEARS OF THE PERITONEAL EXUDATE

Smears were made in eighty-three of the cases in this series, but were omitted in twenty-three examinations, usually when the specimens were small in quantity and taken on cotton swabs. No attempt was made to classify the organisms seen on the slide other than to group

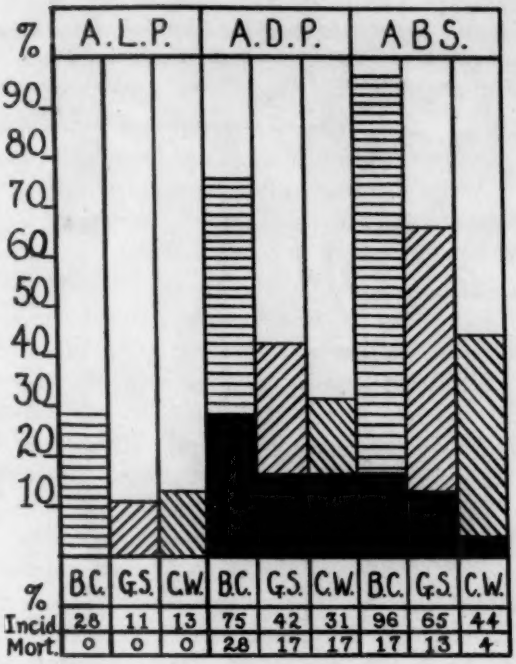

Chart 1.—Incidence and mortality of B. coli, green streptococci and C. welchii in the three main peritonitis groups. *A.L.P.* indicates acute local peritonitis; *A.D.P.*, acute diffuse peritonitis; *ABS*, abscess. The shaded area indicates the percentage of patients who survived; the solid area, the percentage who died.

them into cocci or bacilli and to note whether or not they retained the gentian violet of the Gram stain, because it is absolutely impossible to classify more accurately organisms which are present in exudate, the pleomorphic and the degenerated forms, making a single species appear like several and the identical appearance of different species making many species appear as one. We cannot be sure therefore in many cases whether or not we cultivated all of the organisms that we saw, but this rough differentiation in the comparison of smear and

culture seems to have been profitable. In correlating the smears with the final cultures, it is found that they fall into four groups, which will be analyzed to determine, if possible, whether they bear any relationship to the symptoms and signs presented or have any prognostic significance (table 9).

Cases Showing No Organisms on Smear and Yielding No Growth.—Twenty-five cases fell into this group, seventeen of which were due to appendicitis. Over 80 per cent of the patients came to the hospital within forty-eight hours and 60 per cent within twenty-four. Eighty

TABLE 9.—*Analysis of Certain Important Data with a Correlation of Smears with Growth of Bacteria from the Peritoneal Fluid*

	S0=G0		S>G		S<G		S+=G+	
	No.	%	No.	%	No.	%	No.	%
Total	25		7		24		27	
Time								
12 hours	7	28*	0	0	4	17*	1	4
24 hours	8	32*	0	0	7	29*	4	15*
48 hours	6	24*	1	14*	3	13*	5	19*
72 hours	1	4	2	29*	3	13*	5	19*
96 hours	0	0	1	14*	3	13*	3	11*
96+ hours	3	12	3	43*	4	17*	9	33*
Quadrant 1	13	52*	7	100*	7	29*	6	22*
Quadrant 2	8	32*	0	0*	6	25*	5	19*
Quadrant 3	3	12	0	0	2	8*	2	7*
Quadrant 4	1	4	0	0	9	38*	14	52*
Mild	14	56*	1	14*	4	17	5	18
Moderate	10	40*	6	86*	15	62*	11	41*
Severe	1	4	0	0	5	21*	11	41*
Sequelae 0	18	72*	5	72*	4	17	12	46*
1 to 3	7	28	1	14	13	57*	10	38*
4 to 7	0	0	1	14	6	26*	4	15
Recovered	25	100*	7	100*	19	79	20	74
Died	0	0	0	0	5	21*	7	26*
Fluid								
Little	19	76*	0	0	8	33	6	22
Much	6	24	7	100*	16	67*	21	78*
Clear	7	28	0	0	0	0	0	0
Turbid	18	72*	1	14	14	58*	14	52*
Thick	0	0	6	86*	10	42*	13	48*
Odor								
None	20	100*	1	20	14	77*	7	31
Foul	0	0	3	60*	1	6	9	39*
Fecal	0	0	1	20	3	17	7	31*

per cent of the cases of appendicitis had a typical history. Gastric and intestinal symptoms were minimal. On physical examination, over half of the cases had signs limited to one quadrant, and in 84 per cent they were limited to one or two. The total white cell count was usually high, with polymorphonuclears relatively low, indicating a good resistance against a mild infection. Over one half of the patients were considered to be only mildly ill on admission to the hospital, and all but one of the rest were only moderately ill. All of these patients recovered; 72 per cent had no sequelae and the rest only a few. The great majority left the hospital within fifteen days. In three fourths of the cases the fluid was small in quantity. In one fourth it was described as being clear, in the rest turbid and in none thick. In all of the cases recorded (twenty) there was no odor.

Cases Showing Forms on Smear, Some of Which Did Not Grow Out.—This is a small group of seven cases, and the figures are therefore less reliable than in the other groups. Six of the cases were due to appendicitis, and in five an abscess had formed. Four of the smears showed gram-positive cocci with gram-negative bacilli, and the cocci failed to grow. One showed cocci with both gram-positive and gram-negative bacilli, and the cocci failed to grow. Two showed gram-positive bacilli, together with gram-negative bacilli and gram-positive cocci. The gram-positive bacilli failed to grow. These patients were all late arrivals at the hospital. Three of five had chills. In every case the signs were limited to a single abdominal quadrant. In four of five cases distention was recorded. In six of the seven, a mass was felt. None of the patients was judged to be severely ill on admission. One was mildly, and the rest moderately, sick. All of the patients recovered, and only one had serious complications. Five had no sequelae, although all of them were in the hospital for more than fifteen days. The peritoneal fluid in all of these cases was present in considerable quantity; in all but one it was thick, and in four of five it was odoriferous.

Cases in Which the Peritoneal Fluid Yielded Growth of Organisms Which Did Not Appear on Smear.—This group consists of twenty-four cases, fourteen of which were due to acute appendicitis. In this group the arrival at the hospital was fairly evenly distributed over the time periods, a little over half coming in within forty-eight hours. Seventy-one per cent of the cases of appendicitis had a typical history. On physical examination, only a little over one fourth of the cases had signs limited to a single quadrant, and in three eighths of them four quadrants were involved. Tenderness was constant, rigidity was more frequent than in the preceding group, and the rebound sign was present in about four fifths of the cases when this symptom was recorded. Distention was present in 60 per cent. Total blood counts were low in half of the cases, but the polymorphonuclear percentage relatively high, indicating, perhaps, an increased severity of the infection. Only one sixth of the patients were mildly ill on admission and more than one fifth were considered to be seriously ill. Twenty-one per cent of the patients died, only a sixth were without sequelae, and over one fourth had serious and numerous complications. All who recovered were in the hospital more than fifteen days. The peritoneal fluid was in considerable quantity in two thirds of the cases, turbid in a little over half and thick in the remainder, but no odor was noted in three fourths of the cases.

Cases Showing All of the Forms in the Smear Which Later Appeared in Culture.—There were twenty-seven in this group, twenty-

two of which were due to appendicitis. Sixty-three per cent of the patients came to the hospital after forty-eight hours. Nausea and vomiting were frequent, and fever was invariably present. In a third of the cases recorded there was a history of chill. Only 59 per cent of the cases of appendicitis had a typical history. On physical examination, more than half of these patients showed signs in all four quadrants. Blood counts tended to be low, and the polymorphonuclear percentage corresponded. Forty-one per cent of the patients were judged to be seriously ill on admission to the hospital, and as many more were moderately ill. Only five of the cases were mild. Twenty-six per cent died, although the complications were somewhat less frequent than in the preceding group. The peritoneal fluid was in general more profuse, thicker and much more often odoriferous than in the preceding group.

Comment on the Correlation of Smears of Peritoneal Fluid with Growth of Bacteria.—The first group, in which both smear and growth are negative, evidently represents a condition in which the infecting agents, although sufficiently active in the wall of the organ to call forth a peritoneal reaction and exudation, had not entered the peritoneal cavity in great numbers or multiplied sufficiently to be seen in the smear. The peritoneum was in control of the situation. The symptoms were mild, the sequelae were few, and when the distributing focus was removed, all of the patients promptly recovered. The second group is small and the figures are therefore unreliable, but a general principle is brought out which we believe to be of value. Organisms appeared on smear which failed to grow out. Failure to grow indicated either that they were dead or could not multiply in our culture mediums. If they were dead, they were either killed by the action of the peritoneum or its fluid or died in transit to the laboratory. We know that several of the specimens in this group were planted immediately, and we believe that the organisms were probably destroyed in the peritoneal fluid, which would suggest a resistance on the part of the body to this particular element of the infection. The bactericidal action of these fluids might be subject to experimental demonstration. Runeberg [20] found that it had bactericidal action to a certain degree. In the third group, organisms grew out which did not appear in the smear. These were viable organisms present in small numbers which were capable of multiplying and potentially able to take part, but as yet not actively taking part, in the production of symptoms. In the last group, all of the organism forms seen in the smear were viable and recoverable. Presumably they were active, had already gained a foothold, had been multiplying and had already produced symptoms. Some at least were likely to continue to produce symptoms after the removal of the distributing focus. We believe that if smear and culture are correlated

in every case, the study will be a fair basis for prognosis. If the case falls into the first two groups, the prognosis will be good, if into the third, prognosis must be guarded and depend on special features of the individual case with serious consequences expected in a certain proportion of the cases; if into the fourth group, still more trouble is to be expected.

CULTURES FROM THE PERITONEAL EXUDATE

Our series of cases may be conveniently divided into three groups from the point of view of bacterial growth: those yielding no growth, those yielding from one to three species and those yielding from four to six species. The results are summarized in table 10.

Cases Yielding No Growth.—This group comprises thirty-five cases, three fourths of which were due to appendicitis and the rest to other lesions (table 10). Thirty of these cases were classed as acute local peritonitis and five as acute diffuse peritonitis. There were no cases of peritoneal abscess which failed to yield bacterial growth. We wish to emphasize particularly the following points. Eighty-three per cent of the total number and 92 per cent of the patients with appendicitis came to the hospital within forty-eight hours. Eighty-one per cent of the cases of appendicitis gave a typical history of pain. On physical examination, signs were generally limited to two quadrants; in over one half of the cases the signs were present in only one quadrant. Tenderness was constant, but the rebound sign and rigidity was found in not more than three fourths of the cases. Distention was minimal; no masses were felt, but pelvic tenderness was present in over one half of the cases. The blood count was fairly high in three fourths, and the percentage of polymorphonuclears corresponded. The general impression of the severity of these cases on admission placed 60 per cent in the moderate class. Only one patient was considered to be severely ill. Every patient survived; sequelae were absent or minimal. Over three fourths of the patients left the hospital within fifteen days. The fluid was generally small in quantity, clear or turbid, but never thick; in no case in which this item was recorded was there any odor.

Cases Yielding From One to Three Species of Bacteria.—This group includes forty cases of which, as in the first group, three fourths were due to appendicitis (table 10). On the other hand, only ten of these were classed as acute local peritonitis, while sixteen were called acute diffuse peritonitis, and fourteen were localized peritoneal abscesses. Only a little over half of these patients came to the hospital within forty-eight hours of the onset of the illness. Fever was almost invariably present and chill was a fairly common symptom, being present in half of the cases of appendicitis in which it was mentioned, while nausea and vomiting were considerably more frequent than in

TABLE 10.—*Analysis of Data from the Point of View of the Growth of Organisms from Peritoneal Exudate—One Hundred and Six Cases*

	Growth 0		Growth 1 to 3 Species		Growth 4 to 6 Species	
	No.	%	No.	%	No.	%
Total	35	..	40	..	31	..
Acute local peritonitis	30	87*	10	25	7	23
Acute diffuse peritonitis	5	13	16	40*	15	48*
Abscess	0	0	14	35*	9	29*
Time						
12 hours	7	20*	4	10*	2	6*
24 hours	12	34*	10	25*	7	22*
48 hours	10	29*	7	18*	3	10*
72 hours	1	3	6	15*	5	16*
96 hours	0	0	2	5*	6	19*
96+ hours	5	14	11	28*	8	26*
Nausea +	26	74*	32	80*	28	90*
Nausea 0	9	26	4	11	3	10
Vomiting +	22	65*	30	81*	28	90*
Vomiting 0	12	34	7	19	3	10
Chill +	1	8	10	41*	3	21
Chill 0	12	92*	14	59	11	79*
Fever +	28	82*	38	97*	28	94*
Fever 0	6	18	1	3	2	6
Diarrhea +	3	11	4	14	3	12
Diarrhea 0	24	89	24	86	22	88
Constipation +	9	32	12	36	15	57
Constipation 0	19	68*	21	63*	11	43*
Obstipation +	1	4	1	3	5	19
Obstipation 0	26	96*	32	97*	21	81*
Quadrant 1	20	57*	18	45*	10	32*
Quadrant 2	11	31*	4	10*	9	30*
Quadrant 3	3	3	9	10*	1	3*
Quadrant 4	1	3	14	35*	11	35*
Tenderness +	35	100	40	100	31	100
Tenderness 0	0	0	0	0	0	0
Rigidity +	24	71*	29	85*	22	76*
Rigidity 0	10	29	5	15	7	24
Rebound tenderness +	18	75*	21	87*	15	71*
Rebound tenderness 0	6	25	3	13	6	29
Distention +	2	12	13	48*	19	68*
Distention 0	15	88*	14	52	9	32
Mass +	0	0	13	41*	9	35
Mass 0	28	100*	19	59*	17	65*
Pelvic +	17	57	22	69*	17	57
Pelvic 0	13	43*	10	31	13	43*
White blood cells						
16,000 +	24	73*	23	62*	13	47
16,000 —	9	27	14	38	15	53
Polymorphonuclears						
80% +	23	72*	22	63*	19	73*
80% —	9	28	13	37	7	27
Mild	21	60*	7	18	4	13
Moderate	13	37	24	60*	18	58*
Severe	1	3	9	22	9	29
Sequelae 0	24	69*	15	39*	7	25
1 to 3	11	31	14	37*	14	50*
4 to 7	0	0	9	24*	7	25
Days 15—	27	77*	10	26	4	13
Days 16+	8	23	29	74*	27	87*
Recovered	35	100*	31	78	24	77
Died	0	0	9	22*	7	23*
Fluid						
Little	27	77*	15	37	9	29
Much	8	23	25	63*	22	71*
Clear	9	26*	0	0	0	0
Turbid	26	74	27	68*	15	48
Thick	0	0	13	32	16	52*
Odor 0	24	100*	17	61	8	33
Foul	0	0	5	18*	8	33*
Fecal	0	0	6	21*	8	33*

	Growth Number of Species 1 to 3		Growth Number of Species 4 to 6	
	Number	Per Cent	Number	Per Cent
Total number of cases	40		31	
Anaerobes				
Hemolytic C. welchii	6	15*	21	68*
Nonhemolytic C. welchii	0	0	4	13
Other spore-formers	2	5	4	13
Gram + B. nonspore-formers	2	5	4	13
Gram — B. nonspore-formers	0	0	3	10
Gram + cocci	5	13*	6	19*
Gram — cocci	0	0	1	3
Aerobes				
Hemolytic B. coli	10	25	10	32
Nonhemolytic B. coli	32	80*	30	97*
Green streptococci	14	35*	21	68*
Hemolytic streptococci	4	10	1	3
Nonhemolytic streptococci	9	23*	6	19
Diphtheroid	3	8	8	26*
B. proteus	0	0	6	19*
B. subtilis	1	3	1	3
B. pyocyaneus	0	0	1	3
B. prodigiosis	0	0	1	3
B. mucosus capsulatus	0	0	1	3
Staphylococcus albus	1	3	2	6
Staphylococcus aureus	0	0	2	6
Staphylococcus citreus	0	0	1	3
Leptothrix	0	0	1	3

the first group. In only two thirds of the cases of appendicitis in this group was there a typical history of that disorder. In the majority of the cases the signs were present in more than one quadrant. Tenderness was invariably present, and rigidity and rebound tenderness in from 85 to 87 per cent of the cases. About one half of the patients showed distention. The blood counts were generally a little lower in this group than in the preceding. Only one fifth of the cases were considered mild and almost one fourth were severe. Twenty-two per cent of the cases were fatal. Complications occurred in two thirds of the cases. The peritoneal fluid was present in considerable quantity in almost two thirds of these cases, and in one third it was thick. In two fifths of the cases in which odor was noted, the fluid had a foul or fecal odor. Only eleven of these cases yielded a single species of bacteria; fourteen showed two species and fifteen three. Nonhemolytic *B. coli* was found in 80 per cent and the hemolytic variety in 25 per cent. The green streptococcus was recovered in 35 per cent, the nonhemolytic streptococcus in 23 per cent. *C. welchii* was present in only 15 per cent. Anaerobic streptococci, hemolytic diphtheroid bacilli, *B. subtilis, Staphylococcus albus* and certain nonpathogenic spore-forming anaerobes were present in scattered cases.

Cases Yielding From Four to Six Species.—There were thirty-one cases in this group, two thirds of which were due to appendicitis (table 10). Seven of these cases were classed as acute local peritonitis, fifteen as acute diffuse and nine as abscess. Almost two thirds of these patients came to the hospital after forty-eight hours. Nausea, vomiting and fever were present in over 90 per cent of the cases, but chill was not frequent. More of these cases gave a typical history than those in the two preceding groups. Less than one third had signs limited to one quadrant. Distention occurred in 68 per cent. Blood counts were generally low, with a relatively high polymorphonuclear percentage. Only four of these cases were considered mild on admission, and almost a third were severe. Twenty-two percent of the patients died, exactly the same percentage as in the preceding group, but the complications were more frequent, and the stay of the patients in the hospital was longer than in the cases in the second group. The peritoneal fluid was more frequently profuse and thicker than in the preceding class, and in two thirds of the cases it was recorded as malodorous. Four species were cultivated from the peritoneal fluid from nineteen of these cases, five species from nine and six from three. Nonhemolytic *B. coli* was present in all but one of these cases (a high intestinal perforation). The hemolytic variety was found in 32 per cent. The green streptococcus occurred in 68 per cent and *C. welchii* in the same number, while other bacteria occurred in considerably fewer numbers. A graph

showing the numerical incidence of bacterial species in the cases of appendicitis is given in chart 2.

Discussion of the Data from the Standpoint of Bacteria Grown from the Peritoneal Exudate.—It is evident that in the great majority of cases yielding no growth, the disease is limited to the region of the focus of infection. The peritoneum is in control of the situation, and the organisms, if present, are not viable. With viable organisms present it is not unexpected to find either a diffuse process or a more extensive local process. As one would expect, the duration of symptoms in the group of cases yielding no growth was short, while it was distributed widely in other groups. The symptoms of nausea, vomiting, constipation and obstipation, the physical signs of quadrant involvement and distention,

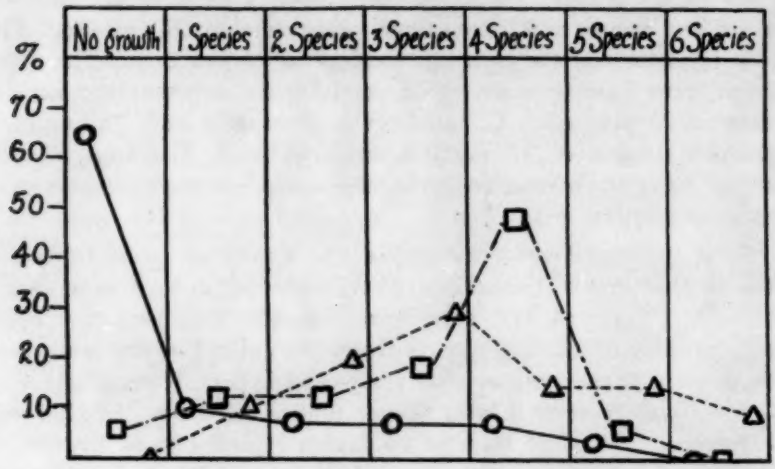

Chart 2.—Curves showing the number of different species of bacteria in the peritoneal exudates of seventy-six cases of appendicitis: acute local peritonitis, thirty-nine cases; acute diffuse peritonitis, seventeen cases; abscess, twenty cases. The circles indicate the cases of acute local peritonitis; the squares, acute diffuse peritonitis; the triangles, abscess.

the white blood cell count, the estimate of severity, the sequelae and the duration of stay in hospital all show progressive changes corresponding to the number of species present in the peritoneal fluid. In certain other respects, namely, in the matter of chill, fever, rigidity, rebound tenderness, mass, pelvic signs and percentage of polymorphonuclears, one finds that in our series, the group with from one to three species gives evidence of being more powerfully affected than the group with from four to six, and when it finally comes to the percentage of fatal cases, the figures are practically the same. This is all the more interesting when we consider that the low mortality of the group with

one species brings down the average of the group with from one to three species. Although this summary seems to show a definite causative relationship between the presence of organisms and the severity of the infection, it is of interest that in our series of cases the reaction of the patients to the presence of from four to six species is not much greater than their reaction to the presence of from one to three species. This cannot be explained on the basis of abscess formation, because as a matter of fact in our series there was a greater proportion of abscesses in the second group. It seems to us that there are at least two possible explanations: beyond three species the organisms are indifferent, without effect and simply saprophytic in the exudate, or with respect to certain symptoms so indicated they are actually antagonistic to the effects of the other organisms with which they are living. They may be antagonistic to certain activities of the other species and protagonistic to others. It is well known that within the intestinal canal various organisms have adjuvant and others inhibiting effects on the activities of their fellow species.

In turning to that portion of the table which lists the species found, one is struck by the prominence of three species, namely, nonhemolytic *B. coli,* green streptococcus and *C. welchii.* In the group with from one to three species, the nonhemolytic streptococcus is also frequent, but when it is remembered that this group merges with the green, its identity is not sufficiently distinct to lay much stress on it. This is less frequent in the group with from four to six species, while the green streptococcus increases almost twofold and the *C. welchii* increases over fourfold. One may be surprised that this fourfold increase of *C. welchii* does not increase the severity and mortality of this group, but this is quite consistent with the observations with regard to this organism in previous summaries made earlier in this paper and adds to the evidence everywhere consistent that this organism is not as serious a factor in peritonitis as it has been considered to be.

GROUPING OF CASES ACCORDING TO CERTAIN SPECIES FOUND IN THE PERITONEAL EXUDATE

It is evident from the preceding summaries that the most frequent organisms found in our series were (1) nonhemolytic *B. coli,* (2) green streptococcus and (3) *C. welchii.* Others of secondary importance were (1) hemolytic *B. coli* (which was never found without the nonhemolytic type being present also), (2) nonhemolytic streptococcus (which, as we have already stated, merges into the green group), (3) anaerobic streptococcus (which in turn merges into the nonhemolytic group), (4) nonhemolytic *C. welchii* (which was never found without the hemolytic type being present also) and (5) diphtheroid bacilli, both aerobic and anaerobic (small gram-positive nonspore-

formers). There is a sufficient number of cases in which the first three organisms were found to warrant grouping, but it must be emphasized that because of the frequency of concurrence, these groups overlap, and certain cases are common to two or all three groups. The comparison may be seen in table 11.

Cases Yielding Nonhemolytic B. coli.—Of the seventy-one cases in the series in which bacteria were found in the peritoneal exudates, sixty-two, or 87 per cent, yielded nonhemolytic *B. coli;* forty-six of these cases

TABLE 11.—*Analysis of Important Data from Cases Yielding B. Coli or Green Streptococcus or C. Welchii*

	B. coli						Green Streptococcus						C. welchii					
	Appendicitis		Others		Total		Appendicitis		Others		Total		Appendicitis		Others		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Totals	46		16		62		24		11		35		15		12		27	
Typical	29	63					15	63					8	53				
Atypical	17	37					9	37					7	47				
Quadrant 1	22	48	4	25	26	42*	9	37	3	27	12	34*	6	40	3	25	9	33*
Quadrant 2	10	22	1	6	11	18*	5	21	2	18	7	20*	5	33	2	17	7	26*
Quadrant 3	2	4	2	13	4	6*	1	4	1	9	2	6	0	0	0	0	0	0*
Quadrant 4	12	26	9	56	21	34*	9	37	5	45	14	40*	4	27	7	58	11	41*
W. B. C.																		
16,000 +	25	60	6	43	31	55*	13	62	4	40	17	55*	8	57	4	36	12	48*
16,000 −	17	40	8	57	25	45*	8	38	6	60	14	45*	6	43	7	64	13	52*
Polymorphonuclears																		
80% +	27	66	9	60	36	67*	14	70	4	45	18	62*	10	77	5	56	15	68*
80% −	14	34	4	31	18	33	6	30	5	55	11	38	3	23	4	45	7	32
Mild	9	19	1	6	10	16*	4	17	2	18	6	17*	2	13	1	8	3	11*
Moderate	28	61	7	44	35	57*	15	62	6	55	21	60*	9	60	4	33	13	48*
Severe	9	19	8	50	17	27*	5	21	3	27	8	23*	4	27	7	58	11	41*
Sequelae 0	19	42	1	7	20	34*	11	48	2	20	13	39*	4	27	1	9	5	19*
1 to 3	18	40	7	50	25	42*	8	35	3	30	11	33	7	47	5	45	12	46*
4 to 7	8	17	6	43	14	24*	4	17	5	50	9	27*	4	27	5	45	9	35*
Recovered	40	87	8	50	48	77*	19	79	6	55	25	71*	13	87	6	55	19	73*
Died	6	13	8	50	14	21*	5	21	5	45	10	29*	2	13	5	45	7	27*
Fluid																		
Turbid	23	50	11	69	34	55*	9	37	8	73	17	49*	6	40	7	58	13	48*
Thick	23	50	5	31	28	45*	15	63	3	29	18	51*	9	60	5	42	14	52*
Odor																		
None	15	43	8	57	23	47	7	37	6	67	13	46	3	21	3	33	6	26
Foul	11	31	2	14	13	26*	6	32	1	11	7	25*	6	43	2	22	8	35*
Fecal	9	26	4	29	13	26*	6	32	2	22	8	29*	5	36	4	44	9	30*

were due to acute appendicitis (table 11). A little over half of the patients came to the hospital after forty-eight hours. Nausea, vomiting and fever were present in over 90 per cent. Chill was a rather frequent symptom, being present in one fourth of the cases in which it was noted. Sixty-three per cent of the cases of appendicitis gave a typical history of that disease. In sixty per cent, the signs were limited to one or two quadrants. All of the patients had tenderness; four fifths, rigidity; three fourths, rebound tenderness, and five eighths, distention. It is chiefly in this feature of distention that this group differs from the group without bacteria. Blood counts were elevated above 16,000 in only 55 per cent, while two thirds had a polymorphonuclear percentage of over 80. About one sixth of these cases were

considered mild, and a little over one fourth were severe. About one fifth of the patients died, and almost all of those who recovered stayed in the hospital more than sixteen days. In two thirds of the cases there was a considerable amount of fluid, which was simply turbid in a little over one-half, but thick in the rest. In one half of the specimens, no odor was noted, but the rest were either foul or frankly fecal.

Cases Yielding Green Streptococci.—Thirty-five or almost one half of the cases in our series that showed growth yielded green streptococci (table 11). In this group also a majority of the patients came to the hospital late. The percentage of histories of typical appendicitis was identical with that of the group yielding *B. coli.* There were fewer cases in the group in which a single quadrant was involved and more in which four quadrants were involved than in the series yielding *B. coli.* Otherwise the physical signs were very much the same. The total white cell counts were about the same, but the polymorphonuclear percentage was a trifle lower. The severity of the cases of this group is very similar to that of the preceding group, and although the complications were not so numerous there was a definitely higher mortality particularly in the cases of appendicitis. The quantity of fluid was usually greater and it was generally thicker, especially in the cases of appendicitis, although the odor was not strikingly different.

Cases Yielding C. welchii.—Twenty-seven cases yielded *C. welchii,* 38 per cent of the seventy-one specimens of peritoneal fluid (table 11). The patients came to the hospital a little later than those in the preceding two groups. The percentage of histories of typical appendicitis was definitely lower, which may have accounted for the delay in reaching the hospital. The extent of the abdominal signs tended to be a trifle greater, but this is not striking. Less than one half of the cases had a definitely raised total white blood count, but the polymorphonuclears were above 80 per cent in two thirds of the cases. One striking difference between this group and the two preceding is that on admission a much larger percentage of patients were considered seriously ill, although the mortality in this group was not higher than in the streptococcic group, and those who survived were not in the hospital any longer than those in the other groups. The quantity and consistency of the fluid were not markedly different, but the odor was definitely noticed as being more offensive.

Discussion of Data from the Standpoint of the Three Common Bacterial Species.—Table 11, which lists the important features of three groups containing *B. coli,* green streptococcus and *C. welchii,* is shown to demonstrate the uncertainty of drawing conclusions from groups of cases in which there are too many common factors. Fifteen cases yielded both nonhemolytic *B. coli* and the green streptococcus, without

G. welchii; ten cases yielded *B. coli* and *C. welchii* without the green streptococcus; only one case yielded green streptococcus and *C. welchii* without *B. coli,* but sixteen cases yielded all three. The only suggestive points are the increased severity of symptoms, the increased number of sequelae and the increased odor to the peritoneal fluid in the cases yielding *C. welchii,* but there is no increase in mortality. Similarly, inconclusive results are obtained when groups of cases are studied by comparing all of the cases yielding one of these organisms with all of the cases not yielding the given organism. There are too many concurrent organisms to get an idea of the effect of one. The most that can be said is that there seems to be some evidence that the presence of each of these organisms adds to the severity of the course of the disease. This seems to be somewhat more definite with respect to *C. welchii* than with the others. It must be remembered, however, that when one of these organisms was absent, another or both of the others were present, thus increasing the importance of the opposing group. Perhaps the most logical conclusion that can be drawn from the data just presented is that each of these organisms plays a rôle but none of them is outstanding. The importance of any of these species in our series seems to depend more on its prevalence than on its outstanding virulence.

A COMPARISON OF CASES FROM THE POINT OF VIEW OF SYMBIOSIS

It is very difficult to evaluate the effect of any one organism, because when organisms are present, the great majority of cases have more than one species. Only eleven cases yielded a single organism; eight of these were nonhemolytic *B. coli,* two were hemolytic streptococci and one an anaerobic diphtheroid. A hemolytic as well as a nonhemolytic *B. coli* was cultivated in one other case. If this is grouped with the eight yielding pure cultures of nonhemolytic *B. coli,* a small series of nine cases may be conveniently studied and compared with a series of twenty-six cases in which both *B. coli* and some streptococci were present in symbiosis and these in turn with another series of twenty-two cases in which *B. coli,* some streptococci and *C. welchii* were present.

Cases Yielding Pure Cultures of B. coli.—Of the nine cases in this group, eight were due to appendicitis and the other to volvulus. None of the patients came to the hospital within twelve hours, and a little over half came after forty-eight hours. Nausea and vomiting were present in all, but in one case there was no fever. Chills were rather common, being present in half of the cases in which the symptom was noted. Three fourths of the cases of appendicitis give a typical history. Intestinal symptoms were minimal, constipation the most frequent, appearing in three of eight cases noted. On physical examination, the signs were limited to one quadrant in seven of the nine cases. Tender-

ness was invariably present, but rigidity was considerably less frequent and rebound tenderness observed in only two cases. Distention was not a prominent feature. The white cell count was elevated in three fourths of the cases, with a corresponding increase in polymorphonuclears. Two thirds of the cases were placed in the moderate group with regard to severity, while two cases were considered mild and only one severe. All of these patients recovered, with relatively mild sequelae and complications, although they were all in the hospital more than fifteen days. A small majority showed a considerable quantity of peritoneal fluid which was more often simply turbid than thick. The fluid was without odor in three and foul in three. In three it was not noted.

Cases Yielding B. coli and a Streptococci without C. welchii.—This group comprises twenty-six cases, twenty-two of which were due to appendicitis; three were classified as acute local peritonitis, fourteen as acute diffuse peritonitis and nine as peritoneal abscess (table 12). These patients as a group came to the hospital a trifle earlier than those in the preceding group, although fewer (two thirds) gave a typical history. The physical signs were much more marked than in the group yielding *B. coli* alone. Only a third had signs limited to one quadrant, and in 50 per cent three or four quadrants were involved. Tenderness, rigidity and rebound tenderness were almost constant. Distention was present in three fourths of the cases. Blood counts, both total and differential, were a little lower. The patients were considered to be a little more seriously ill as a group on admission. Almost one third of these patients died and almost two thirds of them had serious complications. All but one patient among the survivors stayed in the hospital more than fifteen days. The peritoneal fluid was in general more profuse and thicker, and in four of the cases there was a frankly fecal odor. This group of cases is very similar to the one that follows, except for the fact that it contains four more cases of acute diffuse peritonitis. On this account one would expect this group to show more pronounced symptoms. It must be remembered that in this group of cases, besides *B. coli* and streptococci there were other organisms that may have played a rôle, but the same is true of the group that follows, so that the effect of this common factor may be discounted.

Cases Yielding B. coli, Streptococci and C. welchii.—This group comprises twenty-two cases, thirteen of which were due to appendicitis. Three were classified as acute local peritonitis, ten as acute diffuse peritonitis and nine as peritoneal abscess (table 12). Almost three fourths of the patients came to the hospital after forty-eight hours. Only a little over half of the cases of appendicitis gave a typical history. Nausea, vomiting and fever were almost invariably present, but chills were rare. On physical examination, over half the patients were found

to have signs in four quadrants, although rigidity and rebound tenderness were less frequent than in the preceding group. Distention was a prominent feature. Total white cell counts were frequently low, although polymorphonuclear percentages were generally high. The patients were judged to be more severely ill than in either of the preceding groups. Almost half of them were placed in the severely ill class. About the same percentage of patients died, but those who died and those who survived had more serious complications, and all of those who survived stayed in the hospital over fifteen days. The peritoneal

TABLE 12.—*Analysis of Certain Important Data in Nine Cases with B. coli Alone, in Twenty-Six Cases with B. Coli and Streptococcus without C. welchii and in Twenty-Two Cases Yielding All Three Species*

	B. coli Only		B. coli and Streptococcus		B. coli, Streptococcus and C. welchii	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total	9		26		22	
Typical appendicitis	6	75*	15	68	7	54*
Atypical appendicitis	2	25*	7	32*	6	46*
Quadrant 1	7	78*	9	35*	5	23
Quadrant 2	1	11	4	15*	6	27
Quadrant 3	0	0	4	15	0	0
Quadrant 4	1	11	9	35*	11	50*
White blood cells 16,000 +	5	72*	13	57*	10	48*
White blood cells 16,000 —	2	28*	10	43*	11	52*
Polymorphonuclears 80% +	5	72*	14	58*	13	68*
Polymorphonuclears 80% —	2	28*	10	42*	6	32*
Mild	2	22	5	19	3	14
Moderate	6	67*	16	62*	9	41
Severe	1	11	5	19	10	46*
Recovered	9	100*	18	69*	16	73
Died	0	0	8	31*	6	27*
Fluid						
Little	4	44*	9	35	4	18
Much	5	56*	17	65*	18	82*
Turbid	6	67	15	58	9	43
Thick	3	33*	11	42*	12	57*
Odor						
None	3	50	14	70	4	20
Foul	3	50	2	10	7	35
Fecal	0	0	4	20	9	45

exudate was in general more profuse, and in a much larger percentage it was thick, while in 80 per cent it was either foul or frankly fecal.

Comment on the Data from the Standpoint of Symbiosis.—Table 12 brings out some striking features. The first point is that all of the patients in the first group recovered from the single microbic infection, but the mortality jumped to 31 per cent when the streptococcus and other organisms were present, with the exception of *C. welchii*. In another group the mortality remained about the same when all three organisms were present. On the other hand, in all other categories an addition of *C. welchii* led to an increase of symptoms, signs and sequelae, and the peritoneal exudate was greater in quantity, showed more evidence of cellular activity and the odor became more offensive. There seems to be definite evidence from this study that the polymicrobic

infection is more severe than the monomicrobic; also that *C. welchii* may add to the severity of the illness, but there is no evidence of its preponderent or even important rôle in mortality.

THE UNTOWARD RESULTS

We believe that much information can be gained in a study of this kind by a review of the untoward results either as a group or as individual cases.

Fatal Cases.—There were sixteen fatal cases. This group differs from the group in which recovery occurred in certain significant points brought out in table 13. The pathologic classification is of particular interest. Six of the seventy-six patients with appendicitis, or 8 per cent, died. No patients with appendicitis without perforation, whether acutely inflamed or gangrenous, succumbed. Death was limited to three of the eleven patients with perforated appendixes with acute diffuse peritonitis, two of the twelve in whom an abscess developed and one of the five patients with abscess whose appendix was not seen but was thought to have perforated. The mortality among all the other groups was higher, being 38 per cent in the cases of intestinal lesions, including the three cases of perforated ileum but only one of the five cases of perforated colon. The mortality in the cases in which the gallbladder had perforated was still higher, 50 per cent. In two of the fatal cases, the gallbladder had perforated spontaneously, and in the third there had been leakage of bile either during or after operation. In the miscellaneous group one of eight patients died of a fulminating hemolytic streptococcic acute diffuse peritonitis.

Relation of Death to the Extent of the Process.—If the fatal cases are grouped according to the extent of the process, it is seen that no patient with acute local peritonitis died; twelve, or 33 per cent, with acute diffuse peritonitis died, and four, or 17 per cent, with abscess died. The time of admission into the hospital was no index of prognosis except so far as it was a determinant of the extent of the lesion.

Relation of Death to the Age of the Patient.—Of the thirty-three patients less than 20 years of age, none died, and only three of thirty-three in the next two decades succumbed. Among patients of more advanced years, however, the mortality rate rose rapidly. There seems to be definite evidence that age was an important factor.

Relation of Death to the Symptoms and Signs on Admission.—Fever was the only constant symptom in the fatal cases, while it was absent in ten of the ninety in which recovery occurred. The extent of the abdominal signs was not significant per se as an index. Each of the four fatal cases with abscess falls into a different group according to

TABLE 13.—*Analysis of the Sixteen Fatal Cases Compared with the Ninety in Which Recovery Resulted*

	Died, 16		Recovered, 90	
Totals	**Number**	**Per Cent**	**Number**	**Per Cent**
Age				
0 to 20 years	0	0	34	100*
21 to 40 years	3	9	30	81
41 to 60 years	8	26	23	74
61 to 80 years	5	56*	4	44*
Diagnosis				
Acute appendicitis	0	0	37	100*
Perforated appendicitis, acute diffuse peritonitis	3	37	8	63*
Perforated appendicitis, abscess	2	17	10	83*
Perforated appendicitis (?), abscess	1	20	4	80
Gangrenous appendicitis	0	0	9	100
Volvulus, acute diffuse peritonitis	1	50	1	50
Perforated duodenum, acute diffuse peritonitis	1	50	1	50
Perforated ileum, acute diffuse peritonitis	3	100*	0	0
Perforated colon, acute diffuse peritonitis	1	33	2	67
Perforated gallbladder, acute diffuse peritonitis	3	100*	0	0
Hemolytic streptococcus, acute diffuse peritonitis	1	100*	0	0
Total acute local peritonitis	0	0*	47	100*
Total acute diffuse peritonitis	12	33	24	67*
Total abscess	4	17*	19	83*
Mild	0	0	32	100
Moderate	7	13	48	87
Severe	9	47	10	53
White blood cells 16,000 +	7	12	50	88
White blood cells 16,000 −	8	21	30	79
Polymorphonuclears 80% +	9	15	53	85
Polymorphonuclears 80% −	6	18	27	82
Sequelae 0	0	0	46	100
1 to 3	6	17	36	83
4 to 7	10	62	6	38
Pneumonia	10	67	5	33
Distention	10	38	16	62
Vomiting	8	50	8	50
Shock	6	86	1	14
Ileus	6	86	1	14
Retention of urine	6	46	7	54
Disruption of wound	1	50	1	50
Infection of wound	3	11	24	89
Fluid				
Little	3	6	48	94*
Much	13	24*	42	76
Clear	0	0	9	100*
Turbid	10	15*	58	85*
Thick	6	17*	29	83*
Odor				
?	3	..	27	..
None	6	12*	44	88*
Foul	3	28*	10	72*
Fecal	4	31*	9	69*
Smear (forms seen)				
?	4	..	19	..
0	3	9	31	91
1	1	8	11	92
2	4	20	16	80
3	4	24	13	76
Bacterial growth				
0 species	0	0	35	100
1 to 3 species	9	22	31	78
4 to 6 species	7	23	24	77
B. coli	14	22	50	78
Green streptococcus	10	26	28	74
C. welchii	7	25	21	75
B. coli + green streptococcus	9	29	22	71
B. coli + nonhemolytic streptococcus	4	29	10	71
B. coli + C. welchii	6	27	16	73
B. coli +, streptococcus +, C. welchii +	4	25	12	75
B. coli +, streptococcus −, C. welchii +	2	33	4	67

the number of quadrants involved. In the cases of acute diffuse peritonitis in which signs were found in one quadrant, two patients died and two recovered; in those with signs in two quadrants, one died and four recovered; in three quadrants, seven died and fifteen recovered. The severity of the cases was judged from the symptoms and signs on admission. Of the fatal cases, none was considered mild on the patient's admission, seven were in the moderately severe group, while nine were considered to be very serious. On the other hand, of those cases in which the patients survived, thirty-two were mild, forty-eight were moderate and ten severe. Thus 13 per cent in the moderate group and 47 per cent in the severe group were fatal. The blood counts are of interest, as in the other analyses. Of the thirty-eight cases with a total count below 15,000, eight, or 20 per cent, were fatal, while only seven of fifty-seven, or 12 per cent, with a count above 16,000 were fatal. Similarly, but without quite so much distinction, a higher percentage of cases with a low polymorphonuclear count were fatal, (18 per cent) than those with a high count (13 per cent).

Relation of Death to the Postoperative Sequelae and Complications.—Only one case without sequelae was fatal. Death came quickly within an hour of operation before complications could be noted. It was evidently due to the state of shock present before operation. Recovery occurred in forty-six other cases without sequelae. Of the patients with from one to three postoperative complications, five died and thirty-six recovered, a mortality of 12 per cent. Three of these died within forty-eight hours in a state of shock and two later of pneumonia. Of the sixteen patients having from four to seven postoperative complications, ten died, 63 per cent. Ten of the patients who died had pneumonia, six had ileus, six had retention of urine and five suffered from shock. Nine of the fatal results came in the first six days; these were due primarily to the peritonitis. Five of the other seven patients lingered on from nine to twenty-one days and died primarily from fairly immediate complications of the peritonitis. One died in twenty-eight days and the other in eighty-five days from complications only remotely caused by the peritonitis.

The Relation of Death to the Growth of Organisms from the Peritoneal Exudate.—Bacteria were cultivated from the peritoneal fluid in every fatal case. In nine, there were from one to three different species; in seven, from four to six different species. This contrasts strikingly with the patients who recovered. The peritoneal fluid from them yielded no growth in thirty-five; from one to three species in thirty-five and from four to seven species in twenty-four. In other words, the mortality in thirty-five cases with no growth in the peritoneal fluid was zero. In forty cases with from one to three different species in the

peritoneal fluid and in thirty-one cases with from four to six species in the peritoneal fluid the mortality was 23 per cent. The identical mortality percentage in these last two groups makes one wonder whether or not there is some inhibition of bacterial activity when large numbers of species are present offsetting whatever effect increased numbers might have, or whether the minor species are simply inert and indifferent to the process. When one studies more specifically the bacterial species present, it is found that nonhemolytic *B. coli* was cultivated in fourteen, or 88 per cent, of the fatal cases, green streptococci in ten, or 63 per cent and *C. welchii* in seven, or 44 per cent. None of the other species was present in more than three, or 19 per cent of the fatal cases. All of these other species are apparently of secondary importance, except the hemolytic streptococcus; this organism is rare but of significance when it occurs, for it was found in only four cases in the series and two of these were fatal, one yielding the streptococcus in pure culture.

Comment on Fatal Cases.—The table of fatal cases brings out strikingly several points. First, as to age incidence, whatever indeterminate factors play a part in the defense against peritonitis, youth has something that old age lacks. The nature and extent of the lesion had a profound effect in determining mortality. In the group of cases of appendicitis it is significant that death occurred only when there was a perforation with an escape of intestinal contents into the peritoneal cavity. Without perforation, even when numerous species of bacteria were found viable in the peritoneum, as for example in certain of the cases of acute appendicitis and gangrenous appendicitis, the patients recovered. The question arises as to whether death was the result of actual dosage, i. e., numbers of bacteria, of which we have no measure, or the presence of those intestinal fluids that are so irritating to the skin. Again, is it the digestive activity of these juices or simply their chemical reaction that is detrimental? Every patient with perforated ileum, and only one of the five patients with perforations of the large intestine, died. The ileal contents are alkaline, and the colonic contents are usually acid. What has the reaction to do with it?

It is of interest to note that none of the patients with acute local peritonitis died. One sixth of the cases of abscess would seem to be a higher proportion of fatalities than one would expect. However, when it is remembered that even when there is an abscess there is frequently a certain degree of diffuse peritonitis as well and that in opening an abscess the free peritoneal cavity is often entered, this may not seem too large.

That the damage is largely done before the patients come to the hospital is borne out by the estimation of severity in the fatal cases on their admission. Almost half of the patients who were severely ill on

admission died; only 13 per cent of those who were moderately ill died, and none of those who were mildly ill.

The total white cell count was usually low with the percentage of polymorphonuclears relatively higher, which bears out the clinical experience in other suppurative lesions that turn out unfavorably.

The sequelae are of particular interest. Pneumonia occurred in ten of the fatal cases. It was terminal, to be sure, in some of the cases, but in others it was a factor of importance. Excessive distention and excessive vomiting probably indicated the spread of the peritonitis and were present in practically every patient who survived more than a day or two. Shock, of course, was the chief immediate cause of death in the early fatalities, though in most cases it was due to the degree of the peritonitis.

The bacteriology is our chief interest in these cases. The percentage of mortality increases rapidly when more than one organism is seen in smear or is grown out on culture. Only one patient died (the one with fulminating hemolytic streptococcic peritonitis) when a single species was present, and, surprising as it may seem, the mortality percentage when from four to six species were present was almost identical with that of the group with from one to three species. This has already been discussed. Again, the mortality for the three different groups containing the three common species is shown to be almost identical because of the overlapping and the fact that there was almost always more than one organism in the fatal cases. When these species are found together, either in pairs or all three together, the result is not appreciably altered. *B. coli* is so omnipresent that it is hard to rule out the importance of its presence, but we have no evidence that the presence of *C. welchii* increases the mortality or enhances the severity of the illness, or that either *C. welchii* or the green streptococcus is more effective than any other organism in enhancing the virulence of *B. coli*. Inasmuch as in our series of cases it is impossible to separate the bacteria from the succus entericus, we must not lose sight of the possible rôle that it plays in this malady. The high mortality of perforative lesions is shown graphically in chart 3.

The Factor of Resistance of the Individual in Mortality from Peritonitis.—This is something that is very difficult, if not impossible, to measure. Perhaps the most significant indication of this is the age incidence in the fatal cases. This series, however, offers an interesting comparison of four cases strikingly similar in almost every respect, namely, age, diagnosis, extent of lesion, number and kind of bacteria found, severity of symptoms on admission, etc. Only one of these patients died. The one who died differs from the other three simply in the number of sequelae, among which was a sudden cardiac failure

that was not explained as autopsy was refused. It is possible that his sequelae were the result of some unrecognized mistake in postoperative care, but he was in the ward and therefore subject to the care of the whole staff just as the other patients were. In another group of five similar cases, two died and three recovered without obvious explanation except the general resistance of the patient. One of these patients obviously had a factor of weakness in diseased kidneys. Our data do not give any definite information with regard to the resistance of the patients, but that it may be an important factor in the recovery from peritonitis must constantly be kept in mind.

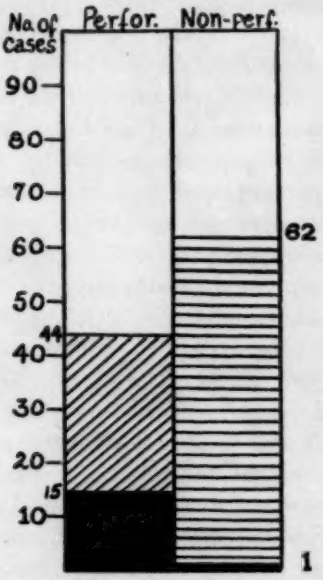

Chart 3.—Incidence and mortality of perforative and nonperforative lesions. The shaded area indicates the number of cases in which recovery occurred; the solid area, the number of fatal cases.

GENERAL SUMMARY

We have studied intensively a small series of 106 cases of peritonitis, and have made a bacteriologic examination of the peritoneal exudate taken at the time of operation. We have studied the conditions at this fixed point of time in the course of a pathologic process and have gone back to the beginning of the illness and on to the end in our clinical study to see what we could logically correlate, in the clinical cinematograph, with the condition at the moment of examination. It would be surprising if we could correlate everything, particularly with the innumerable factors at play both before and after, but with certain

standard methods of procedure it was thought that it would be worth while to make the attempt at correlation and try to interpret our observations. We have studied the question from every angle that seemed to offer any hope of success. We hope that we have not attempted to get more out of our figures than they contain. With so many factors operating, it is only the outstanding features that are of any importance and only consistent results that cannot be explained away. In many respects our results tend to confirm the results of previous workers in this field who established facts that are such common knowledge that they have been the basis of our methods of treatment. In other respects, we are faced with surprising and unexpected results that do not fit our preconceived notions. We should like to emphasize the fact that we were prepared to find all of the known pathogenic spore-forming anaerobic organisms, having spent a considerable period studying their growth requirements before tackling this problem. By the use of blood agar plates and meat medium, *C. welchii* and the other spore-forming anaerobes are particularly easy to isolate and identify. Likewise, the *B. coli* group of organisms are easy to find. There is more difficulty in recovering the intestinal streptococci, because they vary so in artificial medium in their anaerobic requirements and their reaction to hemoglobin in blood agar plates.

Our studies seem to show fairly convincingly the following:

1. The great majority of patients with peritonitis who come to a general hospital have lesions of the appendix. If the inflammation is limited in extent, the peritoneal exudate yields very few organisms on smear or culture.

2. If the appendix has not perforated, the disease is usually not fatal; whether the appendix is gangrenous or simply inflamed, the course is mild and the patients are able to return home in about two weeks.

3. If the appendix has perforated, the inflammation is frequently extensive; the peritoneal exudate is profuse, and yields great numbers of bacteria of several different species. The disease is frequently fatal, the course is stormy, and the patient who survives has to stay in the hospital about twice as long as if it had not perforated.

4. In gangrene of the appendix, we have no evidence from an examination of the peritoneal fluid that the spore-forming anaerobic bacteria either pathogenic or nonpathogenic are particularly active. When perforation of the appendix had taken place, *C. welchii* was found in only twelve of thirty cases, or 40 per cent, whereas *B. coli* was found in every instance. In nine cases of gangrene of the appendix without perforation *C. welchii* was not found once. Of the six fatal cases of perforative appendicitis *C. welchii* was found in only two, or 33 per

cent, which is a lower proportion than its incidence in the whole group of cases of perforated appendix. When we included the cases of perforative appendicitis with the other gangrenous lesions of the appendix, we found that the anaerobes were present in practically the same proportion as in the nongangrenous group.

5. Perforative lesions of the small intestine promptly gave severe symptoms. There was usually extensive tenderness over the abdomen without distention. Total white blood cell counts were frequently low, with a relatively high percentage of polymorphonuclears. In the perforations of the upper intestinal tract, organisms were not usually seen on smear, and early cases yielded no growth. Perforations of the lower small intestinal tract were invariably fatal. The peritoneal exudate was usually profuse and turbid, many organisms were seen, and all yielded bacterial growth. In the nonperforative lesions of the small intestine, the severe symptoms were usually due to signs of intestinal obstruction with or without gangrene of the intestine. In these cases bacteria were usually found on culture in the peritoneal exudate, but smears indicated that they were not present in great numbers, and the patients usually recovered.

6. Perforative lesions of the large intestine in our series caused symptoms to develop more slowly, and in spite of the fact that they occurred in older people and more bacteria were found both in smear and in culture, including *C. welchii* which was invariably present, the large majority of these patients, four of five, recovered.

7. Perforative lesions of the gallbladder in our series were always fatal. The factor of bile irritation seems to be a potent one and several workers have reported that even if sterile, bile will cause a peritonitis which may be followed by the appearance of organisms in the peritoneal exudate.

8. Without respect to the cause of the peritonitis in three fifths of the patients coming to the hospital within twenty-four hours in our series, the lesion was local, the symptoms were mild, the peritoneal exudate was not profuse and organisms were rarely seen in smear or obtained in culture. Diffuse peritoneal inflammation was rarely found in cases with symptoms of less than twelve hours' duration, but usually in later cases. The cases with diffuse peritonitis were more severe, the peritoneal fluid was profuse, and usually many organisms were seen on smear and recovered in culture. Complications were frequent, and a third of the patients died. When abscesses had formed the history was usually of long duration, although symptoms were moderately severe and there was much thick fluid containing many organisms, both on smear and on culture. The mortality was just half that of the diffuse group. Of the three commonest organisms found, namely, *B coli*, the

green streptococcus and *C. welchii,* there is a greater incidence in the diffuse than in the local, and a still greater incidence in the abscess, group. But in spite of the higher incidence, the mortality was less in the abscess group than in the diffuse group.

9. Smears of the peritoneal fluid made at the time of operation and compared with the culture seemed to be of real prognostic importance. When smears showed no organisms and cultures yielded no growth, or when fewer species appeared in culture than were seen on the smear, every patient recovered. These two observations warrant a favorable prognosis. When more kinds of organisms appeared on culture than were seen on the smear, there was an indication that certain organisms were potential of danger. More than one fifth of these patients died. When all of the forms seen on the smear grew out, the mortality was still higher, more than one-fourth perishing. The last two conditions warrant a guarded prognosis.

10. When cases of peritonitis were divided into groups according to the number of bacteria that appeared in the peritoneal exudate, it was found that thirty-five cases yielded no organisms, eleven yielded one, fourteen two, fifteen three, nineteen four, nine five, and three six species. In the great majority of cases yielding no growth, the disease was limited to the focus of infection. With viable organisms present, the majority of patients had acute diffuse peritonitis. With respect to certain symptoms and signs, there was a steady increase of severity corresponding to the number of species present. Other symptoms and signs were more severe in the group with from one to three species than in the group with from four to six. This suggests either that certain species found are inert or that there may be protagonistic effects of one bacterial species on another in the production of certain symptoms and antagonistic effects in the production of other symptoms.

11. There were three outstanding bacterial species in our series of peritoneal exudates. Nonhemolytic *B. coli* was present in 87 per cent of the cases in which bacteria were found, green streptococci were present in 49 per cent and *C. welchii* was present in 38 per cent. Altogether twenty-three different bacteriologic groups were recovered.

12. In our series, peritonitis was usually a polymicrobic disease. In only eleven of the seventy-one cases that yielded growth was a single species found. For that reason it was virtually impossible to evaluate the rôle played by each one. Any grouping to bring out a single factor was nullified by the presence of many common factors. The disease was worse in almost every respect when more than one organism was present than when there was a single organism. The importance of any of these species in our series seems to depend more on its prevalence than on its outstanding virulence. All of the evidence seems to show

that *C. welchii* and the other spore-forming anaerobes as well as the anaerobic streptococci and diphtheroid bacilli do not appreciably increase the severity of the disease or increase the chance of a fatal outcome.

13. There were no fatal cases in the acute local peritonitis group. A third of the cases of acute diffuse peritonitis were fatal. A sixth of the cases of abscess were fatal. All but one of the deaths occurred in cases of perforative lesions in which there was not only a bacterial but a chemical and a foreign body factor. These factors cannot be separated in clinical cases.

14. Every case of perforated ileum was fatal and only one of five in the group with perforated colon. Only one patient with a single infecting organism died; that organism was a hemolytic streptococcus.

15. The mortality percentage when from four to six species of organisms were present was almost identical with that of the group with from one to three species.

16. Although a third of our patients were less than 20 years of age, none of these patients died. In the next two decades only three of thirty died. After the age of 40, the mortality increased considerably with age.

17. Variations in outcome in patients of the same age who seemed to have practically identical pathologic and bacteriologic conditions at the time of operation indicate that the factor of individual resistance to peritoneal infection is an important one and must not be lost sight of.

CONCLUSIONS

1. It cannot be too strongly emphasized that the most important prophylactic treatment for peritonitis, as seen in a general surgical hospital, is early diagnosis and early operation in acute appendicitis.

2. A comparison of smear and culture with the pathologic condition at the time of operation gives a sound basis for prognosis.

3. In the great majority of cases yielding bacteria in our series, there was a polymicrobic infection. In any specific prophylactic or active treatment for bacterial peritonitis one must take into consideration the symbiosis of the commonest organisms found in the peritoneal exudate, namely, *B coli*, the green streptococcus and *C. welchii*.

4. The mortality in perforative cases was so much greater than in the nonperforative cases in our series that the rôle of the intestinal juices must not be forgotten.

5. The results of this study lay the ground work and point the way to some specific experimental studies, of which may be mentioned: (*a*) vaccine and serum prophylactic and active treatment, (*b*) the bacteriostatic effect of peritoneal fluids, (c) the neutralization of digestive ferments and (*d*) the synergisms and antagonisms of certain bacteria.

OXYGEN THERAPY

INSUFFLATION INTO ORAL PHARYNX *

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Dyspnea, cyanosis and other signs and symptoms are, of course, evidence of want of oxygen and are usually abated in a patient who is benefited by oxygen therapy. Clinical experience, however, has led us to believe that reduction of the pulse rate is by far the most reliable single guide by which to judge benefit, or failure of benefit, from the administration of oxygen-rich atmosphere. It is therefore desirable that when oxygen therapy is instituted, as high a concentration as is mechanically available should be first begun. Meanwhile a careful charting of the pulse rate should be made at least every fifteen minutes. With high concentrations, approaching 100 per cent, the pulse rate will probably be reduced during the first few hours. If such an effect is not secured, careful adjustment of the method of administration having been made to assure the operator that an extremely high percentage of oxygen has been displayed at the glottis, effort beyond a few hours is futile, and the attempt should be abandoned. If, however, a definite reduction in pulse rate does take place, reduction of the oxygen flow may then be made until such a point is reached that the maximum reduction of pulse rate is still maintained. This should be chosen as the optimum concentration for that patient, and the interval between pulse rate readings can be lengthened to one hour. At the slightest rise in pulse rate or the return of dyspnea the oxygen concentration should be increased until the maximum clinical effect is again obtained.

When the clinical progress has reached such a point that the necessity for excess oxygen in the inspired atmosphere appears to be no longer indicated, fifteen minute readings of the pulse rate are again instituted, accompanied by gradual small reductions in the concentration of oxygen. Whenever the pulse rate tends to increase, the concentration of oxygen must again be raised. So over a period of from twenty-four to forty-eight hours in the usual case, sometimes more rapidly, oxygen therapy should be gradually discontinued. The physician should at all times bear in mind that the change in atmospheric environment during

* Submitted for publication, March 17, 1930.

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the interruption of oxygen therapy is not unlike that experienced by a person in traveling from sea level to mountain peak. The circulatory muscle of a person whose heart reserve is adequate in ordinary life has occasionally been greatly embarrassed by such a change. Nothing short of an elevator or airplane ascent could simulate the rapidity with which reduction in percentage of oxygen takes place during sudden withdrawal of oxygen therapy. In certain instances extremely gradual reduction to normal atmospheric conditions has been found necessary.

Administration of excess oxygen by means of a catheter passed through the nares is one of the simplest and most generally available methods. As to the efficiency of this technic, opinions expressed in the literature are at extreme variance. Evans [1] recently compared the nasal catheter to the old-fashioned funnel suspended over the patient's face and attached to a small oxygen tank and wash bottle through which 200 or 300 cc. of oxygen a minute were allowed to flow. McCleod and others have, of course, long since called attention to the absolute inefficiency of the funnel method. On the other hand, Barach [2] recently showed that inspired oxygen can be raised to above 35 per cent by allowing 5 liters of oxygen to flow through a nasal catheter. A more or less superficial experience with oxygen therapy by this means over a period of ten years, together with observations in the routine administration of several anesthetic agents, mixed with oxygen in various percentages, by pharyngeal insufflation, led to the impression that much higher percentages could be reached than those reported by Barach.

In administering anesthetic gases and vapors by pharyngeal insufflation, the position of the tip of the catheter in the pharynx has proved important. Efficient anesthesia cannot be maintained with minimum quantities when the delivery is in the nasopharynx. Even with a maximum flow of gases, when the tip of the catheter is in the nasopharynx, the gases flow in one nostril and out the other or around the catheter rather than pass the soft palate into the oral pharynx and to the glottis. To maintain efficient anesthesia by means of pharyngeal insufflation, the catheter tip must be inserted well into the oral pharynx, the nearer the glottis the better. Similar physical principles are involved in the pharyngeal insufflation of oxygen. The therapeutic use of pharyngeal insufflation, however, often necessitates passing the catheter through the nostril of a semiconscious or noncooperative patient. The tip of the catheter must lie in an oral pharynx in possession of normal reflexes. Great care and sometimes considerable diplomacy is necessary in successfully placing and fixing the catheter in proper position.

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1. Evans, John: Am. Med. **24**:211, 1929.

2. Barach, A. L.: Administration of Oxygen by Nasal Catheter, J. A. M. A. **93**:1550 (Nov. 16) 1929.

In order to determine whether high concentrations of oxygen could be maintained at the glottis of conscious patients by means of pharyngeal insufflation, the following experiments were performed.

EXPERIMENTS

Rubber urethral catheters no. 8 or 10 F. were used. Each catheter was perforated with four extra holes in the terminal half inch as suggested by Barach.[2] Multiple openings prevent the possibility of a constant stream of oxygen striking

Oral Pharyngeal Insufflation of Oxygen, Showing Quantity of Oxygen Flowing and Gas Analyses of Samples Taken Near Glottis

Oxygen, Cc. per Minute	Inspiration		Expiration		Comment
	Oxygen	Carbon Dioxide	Oxygen	Carbon Dioxide	
1,500	26.0	0.2	23.0	4.2	Catheters 4½ to 5½ inches from exterior nares
2,200-1,800	29.8	...	25.4	4.2	Nasal breathing
2,200-1,800	27.5	0.5	25.0	3.8	Oral breathing
2,800-2,720	....	...	34.6	4.0	Oral and nasal breathing
4,200-3,100	....	...	36.1	4.1	Oral and nasal breathing
4,200-4,120	....	...	37.8	4.0	Oral and nasal breathing
4,800	45.7	...	....	...	Oral and nasal breathing
5,200-4,400	50.0	0.4	41.0	4.0	Oral and nasal breathing
4,800	54.7	0.7	....	...	Nasal breathing
6,180	39.0	...	43.0	4.3	Catheters withdrawn slightly
8,400	53.0	...	53.0	4.6	Catheters withdrawn slightly
6,000	....	...	72.4	2.6	Catheter beyond 5 inches; mouth closed; gas swallowed
6,000	....	...	70.0	2.6	Same as preceding observations
6,000	....	...	71.1	2.6	Catheter 4½ to 5 inches, from exterior nares; nasal breathing; no gas swallowed
6,000	....	...	71.6	2.2	Same as preceding observations; oral breathing
10,000	74.2	0.2	....	...	Catheter 4½ to 5 inches from exterior nares; mouth closed

one spot on the pharyngeal mucosa and thus annoying the patient and irritating the membrane. The likelihood of blocking the one opening when negative pressure is applied in taking samples from the pharynx is also obviated. The sample catheter was inserted through the nostril and down the posterior wall of the pharynx to a point opposite the glottis or nearly so. The taking of tracheal samples seemed unjustifiable in conscious patients. The delivery catheter was inserted in the other nostril with oxygen flowing. It was advanced slowly down the oral pharynx until the subject found that a bolus of oxygen was swallowed during the act of deglutition. (A cooperative subject easily determines this point. The fact that gas is swallowed during deglutition is, however, very evident to the observer.) The catheter was then slightly withdrawn until no gas was swallowed during deglutition. This point had been previously found to be the optimum position to secure good clinical results in oxygen therapy.

With "sample" and "delivery" catheters placed as described, a known volume of oxygen per minute was allowed to run through the delivery catheter, and samples were taken by means of negative pressure applied for short periods during each respiratory cycle, from two to four minutes being consumed in taking each sample.

The resulting analyses of these samples with the number of cubic centimeters of oxygen per minute flowing through the delivery catheter are set forth in the accompanying table. Notes are added in some cases, as to the time samples were taken in the respiratory cycle, and whether the mouth was closed or open.

Certain facts are evident from these experiments:

1. The possibility of administering oxygen in concentrations in excess of 70 per cent by means of a catheter placed in the oral pharynx of a conscious patient is established. A flow of from 7 to 8 liters per minute is capable of maintaining a percentage well in excess of 50 at the glottis.

2. Whether the mouth is open or closed has much less effect on the concentration of oxygen at the glottis than does the position of the catheter and the rate of flow of the oxygen.

3. The position of the delivery tip of the catheter is very important. Careful fixation of the catheter with adhesive strips is essential to the comfort of the patient. When properly placed and properly fixed almost no sensation is experienced by the subject other than one of comfort and ease in breathing. The position of the catheter does not seriously interfere with swallowing of food or with speech.

4. The catheter, once ideally placed, should be marked at the exterior nares in order properly to place a fresh catheter at twelve hour intervals in the alternate nostril. The proper distance of the catheter tip from the exterior nares, in the subjects used for these experiments, varied between 4½ and 5½ inches (11.4 and 13.9 cm.). Viewed through the mouth this position was usually about level with the tip of the uvula as it hung quiescent during nasal breathing.

5. Small urethral catheters of a size not to exceed 10 French are ideal for this purpose, but, as suggested by Barach, they should carry extra holes punched in the terminal half inch.

COMPARATIVE ADVANTAGES AND DISADVANTAGES

Consumption of Oxygen.—By means of the pharyngeal catheter, properly placed, concentrations of oxygen at the glottis in excess of 50 per cent can be maintained with a flow not exceeding 7 liters. Reports from clinics (Columbia Hospital, Milwaukee, and the Mayo Clinic, Rochester, Minn.) using oxygen chambers estimate the volume of oxygen used as from 7 to 8 liters per minute to maintain concentrations between

50 and 60 per cent. Roth [3] reported that a flow of from 5 to 6 liters per minute will maintain from 50 to 60 per cent concentration in the oxygen therapy tent, provided the tent flaps are kept carefully tucked in and no leaks are permitted. Evans [1] reported the consumption of oxygen to be as great when a face mask is used. By the use of soda lime absorption of carbon dioxide and a closed inhaler and breathing bag, we have been able to administer pure oxygen atmosphere to a patient at forty-five minute intervals over a fifty-four hour period with an average consumption of 620 cc. per minute. Such a method, however, we believe to be applicable only to patients with chronic conditions who are not annoyed by a tightly fitting face mask.

Cost of Equipment.—The equipment necessary for the use of catheters is cheap and easily procured wherever compressed gases are used. Tanks and pressure-reducing gages can often be rented for short periods. The original cost of chambers for oxygen therapy has been estimated at from $3,000 to $5,000 per bed. Tents require less large original investments.

Supervision.—The catheter technic requires great care as to proper fixation of the tube and as to maintaining a sufficient flow of oxygen. Nursing care is not embarrassed in any way. Chambers require careful mechanical maintenance of carbon dioxide removal and moisture regulation. Nursing care is ideally easy, but expensive. In the use of tents extreme care is necessary to maintain the concentration of oxygen in the face of the necessity for raising tent flaps during feeding, expectoration, etc.

In conclusion, evidence is presented to show that, with proper care in placing catheters in the oral pharynx barely short of the point at which swallowing of gas occurs during deglutition, ample concentrations of oxygen can be maintained in the inspired atmosphere to accomplish satisfactory clinical results.

3. Roth, Paul: J. Lab. & Clin. Med. **12**:388, 1928.

THE RÔLE OF TOXIN OF BACILLUS WELCHII IN THE TOXEMIA OF ACUTE INTESTINAL OBSTRUCTION

AN EXPERIMENTAL STUDY *

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The presence of bacteria in the lumen of an obstructed bowel is necessary for the production of the lethal substances that produce the toxemia of acute intestinal obstruction. This bacterial origin of the toxin in the content of the obstructed bowel is being universally accepted. It has been amply proved by the investigations of Murphy and Vincent,[1] Murphy and Brooks,[2] Brooks, Schumacher and Wattenberg,[3] Dragstedt, Moorhead and Burcky,[4] Dragstedt and Moorhead,[5] and Dragstedt, Dragstedt, McClintock and Chase.[6]

The exact nature of the toxins formed in the obstructed bowel is not known. In 1918 Dragstedt, Dragstedt and Chase [7] concluded that no immune bodies are produced following the repeated injection of fluid from obstructed loops of bowel into the veins of rabbits. A further conclusion from their study was that the toxic properties of this fluid are probably not of protein nature. Before these workers injected the

* Submitted for publication, April 14, 1930.

* From the Department of Surgery, Indiana University School of Medicine.

* Aided by a Grant from the Committee on Scientific Research of the American Medical Association.

1. Murphy, F. T., and Vincent, Beth: An Experimental Study on the Cause of Death in Acute Intestinal Obstruction, Boston M. & S. J. **155**:684, 1911.

2. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Causes of Symptoms and Death, Arch. Int. Med. **15**:392 (March) 1915.

3. Brooks, B.; Schumacher, H. W., and Wattenberg, J. E.: Intestinal Obstruction: An Experimental Study, Ann. Surg. **67**:210, 1918.

4. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: Intestinal Obstruction: I. An Experimental Study of the Intoxication in Closed Intestinal Loops, J. Exper. Med. **25**:421, 1917.

5. Dragstedt, Carl A., and Moorhead, J. J.: Immunity in Intestinal Obstruction, J. Exper. Med. **27**:359, 1918.

6. Dragstedt, L. R.; Dragstedt, Carl A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, J. Exper. Med. **30**:109, 1919.

7. Dragstedt, Carl A.; Dragstedt, L. R., and Chase, C. S.: The Antigenic Property of Closed Intestinal Loop Fluid, Am. J. Physiol. **46**:366, 1918.

toxic fluid into the rabbits, they heated it to 70 C. on a water bath for an hour. An interest in heat-labile toxins of fluid in the obstructed bowel has been stimulated by researches conducted since these communications were made.

Williams,[8] a British surgeon, advanced the hypothesis that the toxin of *Bacillus welchii* is the toxic agent in acute intestinal obstruction. Some strains of this organism produce a powerful myotoxin which is heat-labile. In support of his theory, Williams pointed to the similarity between the clinical pictures of intestinal obstruction and of *B. welchii* infection. He found the organisms in the vomitus from patients with obstruction, demonstrated the presence of the toxin in the filtrate of the content of the obstructed bowel by animal inoculation and lowered the mortality rate clinically by giving *B. welchii* antitoxin to groups of patients with intestinal obstruction and peritonitis.

Bower and Clark,[9] and Morton and Stabins [10] submitted clinical and experimental evidence of the therapeutic value of *B. welchii* antitoxin in acute intestinal obstruction and peritonitis. Stabins and Kennedy [11] demonstrated that a rapid growth of *B. welchii* organisms occurred soon in isolated loops of bowel from which they failed to culture such organisms before the obstruction was produced. McIver, White and Lawson [12] found from cultural studies of the bacterial flora of the obstructed loops of bowel in cats that the number of *B. welchii* organisms was always so increased that there was no doubt that this was the predominant organism.

McClintock and Hines [13] studied the occurrence of heat-labile toxins in closed intestinal loops. They injected the Berkefeld filtrate of the loop fluid intraperitoneally, using two series of guinea-pigs. In one series the unheated filtrate was used; in the other, an equivalent amount of filtrate heated for one hour to 65 C. was injected into the peritoneal cavity. In six animals that received the unheated fluid, death occurred in from twelve to forty-eight hours. In six control animals the heated fluid failed to cause marked toxemia or death. They failed to demon-

8. Williams, B. W.: The Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction and Peritonitis, Brit. J. Surg. **14**:295, 1926.

9. Bower, J. O., and Clark, J.: Bacillus Welchii Antitoxin: Its Therapeutic Value, Am. J. M. Sc. **176**:97, 1928.

10. Morton, J. J., and Stabins, S. J.: Experimental Studies on the Relation of Bacillus Welchii Antitoxin to the Toxemia of Acute Intestinal Obstruction, Arch. Surg. **17**:860 (Nov.) 1928.

11. Stabins, S. J., and Kennedy, J. A.: The Occurrence of Bacillus Welchii in Experimental High Intestinal Obstruction, Arch. Surg. **18**:753 (Feb.) 1929.

12. McIver, M. A.; White, J. C., and Lawson, G. M.: The Rôle of the Bacillus Welchii in Acute Intestinal Obstruction, Ann. Surg. **89**:647, 1929.

13. McClintock, J. T., and Hines, H. H.: The Occurrence of Heat-Labile Toxins in Closed Intestinal Loops, Proc. Soc. Exper. Biol. & Med. **26**:654, 1929.

strate the presence of the toxin of *B. welchii* in the fluid of the obstructed loops.

Scholefield [14] confirmed the observations of Sugito [15] that blood withdrawn during the last moments of life from radicles of the portal vein draining an obstructed loop of the intestine of the dog is toxic for mice. While the serum was separating, it was kept at a low temperature and then was injected into the peritoneal cavity of mice. It killed them in from three to fourteen hours. The serum from normal dogs was not toxic for mice when given in similar quantities.

Prati [16] used the supernatant fluid from a centrifugated extract of feces from both the normal and the occluded bowel of dogs. He injected this subcutaneously into guinea-pigs, using a control series protected by *B. welchii* antitoxin. He found that *B. welchii* antitoxin reduced materially the toxicity of these extracts. When the extract of the content of the occluded bowel was given, the animal lived for an average of eight hours. When given the extract to which *B. welchii* antitoxin was added, the animals lived for an average of twenty-two hours.

The exotoxin produced by *B. welchii* contains both a myotoxin and a hemolysin, as shown by Bull and Pritchett [17] and by Henry.[18] This exotoxin is weakened when it is exposed to the air, and it is destroyed by heating to 70 C. for thirty minutes. Animals subjected to sublethal doses of the exotoxin produce an antitoxin that is monovalent. The antitoxin neutralizes this toxin in multiple proportions and the hemolysin as well as the myotoxin is neutralized.

The myotoxin, strongest in fresh cultures from twelve to twenty-four hours after inoculation, may disappear on the second or third day

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14. Scholefield, B. G.: Acute Intestinal Obstruction: Experimental Evidence of the Absorption of Toxin from the Obstructed Bowel, with a Critical Review of Various Methods of Treatment, Guy's Hosp. Rep. **77**:160, 1927.

15. Sugito, Su: Ueber die Todesursache bei Ileus, Mitt a. d. med. Fakult. d. k. Univ. Kyushu Fukuoka **9**:229, 1924, quoted by Scholefield (footnote 14).

16. Prati, Mario: The Presence of Perfringens Toxin in the Contents of the Normal and Occluded Intestine, Boll. d. Ist. sieroterap. milanese **8**:165 (March) 1929.

17. Bull, Carroll, G., and Pritchett, Ida, W.: The Toxin and Antitoxin of and Protective Inoculation Against Bacillus Welchii, J. Exper. Med. **26**:119, 1917; The Prophylactic and Therapeutic Properties of the Antitoxin for Bacillus Welchii, ibid. **26**:603, 1917; Identity of the Toxins of Different Strains of Bacillus Welchii and Factors Influencing Their Production in Vitro, ibid. **26**:867, 1917.

18. Henry, Herbert: On B. Welchii Hemotoxin and Its Neutralization with Antitoxin, J. Path. & Bact. **25**:1, 1922; The Precipitation of B. Welchii Toxin, ibid. **23**:273, 1919, 1920; On the Composition of B. Welchii Toxin, ibid. **26**:497, 1926.

(Henry [19]). Reed and Spence,[20] and Barach and Draper [21] demonstrated an antihemolysin in rabbits three weeks after the injection of small amounts of the toxin of *B. welchii*, its maximum in seven weeks and persistence for a year. Henry [19] reported that the amount of antitoxin necessary to protect mice against the myotoxin is much less than that necessary to neutralize the hemolysin.

EXPERIMENTAL STUDIES

In these studies experiments were made to secure evidences directly as well as indirectly of the absorption of the toxin of *B. welchii* from closed intestinal loops produced in dogs.

1. B. Welchii Antitoxin in Dogs with Isolated Intestinal Loops.—In thirty-five strong, medium-sized, short-haired dogs a loop of jejunum was isolated and an end-to-end anastomosis of the bowel was made. Each animal was given 1 grain (0.066 Gm.) of morphine sulphate subcutaneously and ether anesthesia. The jejunum was transected 10 cm. below the ligament of Treitz, and loops from 15 to 35 cm. long were isolated. The Parker-Kerr [22] technic of end-to-end anastomosis was used to establish the continuity of the intestine. The ends of the isolated loop were closed by the Parker-Kerr technic, care being used to turn in no more of the bowel end than was absolutely necessary. Many of the animals, at the beginning of the study received by hypodermoclysis 0.5 liter of normal physiologic solution of sodium chloride. This was not continued, for it was found that they recovered well from the operation without it. All of the animals were given as much food and water as they cared to take.

Twenty of the animals were given 5 cc. of concentrated *B. welchii* antitoxin daily from the day of the operation until their death. The only exception to this was due to a temporary shortage of the antitoxin when two or three animals missed their dosage for a day or two. The antitoxin was given subcutaneously and the injections were begun on the day of operation. It was supplied by the Mulford Company and was standardized so that 1 cc. would neutralize 5,000 minimal lethal doses of the toxin of *B. welchii*.

The fifteen animals in the second series were treated exactly as the animals of the first series, except that they received no antitoxin. Three of these animals, one of the protected series (no. 65) and two of the control series (nos. 38 and 64), recovered well from the operations, and ate heartily but became progressively emaciated. Finally anorexia developed. When it seemed that the animals would die soon, the abdomen was reopened and the isolated loop was removed. The conditions in these three animals were most interesting and are considered in section 4 of this paper. The loops were resected on the twenty-sixth day, the forty-third day and the sixteenth day, respectively, after operation. In striking

19. Henry (footnote 18, third reference).

20. Reed, G. B., and Spence, M.: Duration of Immunity to Bacillus Welchii Toxin (in Rabbits), J. Infect. Dis. **41**:428, 1927.

21. Barach, A. L., and Draper, G.: Studies in Experimental Anemia: Immunologic Study of Relation Between Pernicious Anemia and Anemia Due to Welch Bacillus Toxin, J. Clin. Investigation **4**:539, 1927.

22. Kerr, Harry H.: The Development of Intestinal Surgery, J. A. M. A. **81**:641 (Aug. 25) 1923.

an average length of life after operation for comparison, the day the loop was resected was considered as the day of death.

Postmortem examinations of all the animals were made to determine the cause of death. In five of the dogs receiving antitoxin a simple obstruction was found. In four animals this was caused by invaginating too much bowel wall when the end-to-end anastomosis was performed in the first group of operations, and was due to inexperience with the type of technic used. The simple obstruction in the fifth dog was due to a hairy bezoar. These dogs lived for 10, 10, 14, 8 and 24 days. At postmortem examination in none of these was the loop ruptured and there were evidences in each of dehydration and starvation. The mucosa within the loop was intact and there was no necrosis of its wall. In two of them the loop was extremely flabby and its content quite pasty, owing to absorption of fluid.

TABLE 1.—*Length of Life of the Animals After Operation*

Number of Animals	Condition	Duration of Life, Days	Average Duration of Life of Whole Group, Days	Average Duration of Life of Animals With Toxemia and Peritonitis, Days	Average Duration of Life of Toxemic Animals, Days
Series A: Animals Receiving B. Welchii Antitoxin (20 Dogs)*					
1	†Toxemia and resected loop	26	...	...	...
4	Toxemia and unruptured loop	2, 2, 3, 1	...	...	...
10	Toxemia and ruptured loop	2.5, 4, 2, 10, 8, 4, 2, 3, 3, 3	...	...	...
5	Toxemia and simple obstruction	8, 10, 10, 14, 24	...	...	...
			7.0	3.5	2.0
Series B: Control Animals (15 Dogs)					
2	†Toxemia and resected loop	43, 16	...	...	...
5	Toxemia and unruptured loop	5, 2, 2, 5, 3	...	...	...
8	Toxemia and ruptured loop	1.25, 2, 4.5, 1.5, 4, 5, 3, 6	...	...	...
			6.8	3.4	3.4

* No beneficial effects from the administration of B. welchii antitoxin were observed.
† The duration of life of these animals was taken up to the time of the resection of the loop.

Four of the twenty animals that received antitoxin died. Autopsy disclosed an unruptured loop enormously distended, discolored and with a necrotic mucosa but no gross evidence of peritonitis. In each dog there was a serosanguineous transudate free in the peritoneal cavity. The average length of life of these animals was two days.

The characteristic features of the conditions found at autopsy in the animals with ruptured loops were those found by van Beuren.[23] The loops had been enormously distended. They were discolored with purple to black gangrenous patches and with perforations opposite the mesentery. A virulent peritonitis had occurred in some. In others the animals were apparently overwhelmed by rapid absorption of toxins from the liberated loop fluid before peritonitis developed.

The average length of life of the "protected" series was 7 days and that of the control series 6.8 days. Removing from consideration the anmials from which the loop was resected and those having simple obstruction, the average length

23. Van Beuren, F. T.: The Mechanism of Intestinal Perforation Due to Distention, Ann. Surg. **83**:69, 1926.

of life of the fourteen protected animals was 3.5 days and that of the thirteen control animals 3.4 days.

Five of the control animals died with an unruptured loop and with evidence of acute toxemia. The average length of life of these animals was 3.4 days, 1.4 days longer than the average of the same group of the series receiving *B. welchii* antitoxin.

2. The Immunization of Dogs by B. Welchii Toxin.—A series of eight short-haired dogs of uniform size were inoculated with the toxin of *B. welchii.* A toxin, made by Dr. H. W. Cromwell, from a virulent strain of *B. welchii,* was supplied by the Swan-Myers Company. The minimal lethal dose of each lot of toxin was determined by intramuscular injection into pigeons. The animals were given six injections of toxin made at weekly intervals. The first injection was made intramuscularly and consisted of a sufficient quantity of the Berkefeld filtrate of a broth culture to contain 5 minimal lethal doses. Following two or three injections there was a marked local reaction. After the second dose of the filtrate further immunization was carried out by intravenous injections of the unfiltered cultures. The dosage was gradually increased until a final dose of 12 minimal lethal doses was given. Some of the culture occasionally escaped into the areolar tissue along the vein, but no local reaction was produced. One of the eight animals died from distemper, and another following a fight; a third was not used because it was ill.

Seven weeks after the first inoculation of *B. welchii* toxin was made, five of the eight animals were bled and their serum was used in an attempt to protect pigeons against lethal doses of *B. welchii* toxin as well as in tests for hemolysis.

The serum was kept at icebox temperature until the tests were made. For the inhibition of hemolysis tests an eighteen hour broth culture of *B. welchii* with a p_H of 7 was centrifugated at high speed for an hour. The serum from the dogs was mixed with the supernatant fluid from the centrifugated broth culture and incubated for one hour on the water bath at 56 C. A 5 per cent suspension of rabbit red blood cells, washed with Ringer's fluid was added to the serum and toxin, and the serum-toxin mixture was again incubated for an hour. Adequate controls were employed. Two of the five animals gave no evidence of anti-hemolysin in their serum. The serum from two dogs gave complete protection, and one gave partial protection, against hemolysis (table 2).

The serum from the two dogs giving strong protection against hemolysis also protected pigeons for forty-eight hours or longer against 23 and 24 minimal lethal doses of *B. welchii* toxin, respectively. The serum containing moderate quantities of antihemolysin protected a pigeon for more than forty-eight hours against only 2.4 minimal lethal doses. Serum from the animals that contained no antihemolysin did not protect pigeons against 1 minimal lethal dose of the toxin.

Isolated loops, from 30 to 45 cm. long, were produced in these three animals in the same manner as in the animals reported in section 1. One animal died after forty-eight hours with a ruptured loop and general peritonitis, and another after nine days with the same conditions. The serum of this animal gave the least protection to a pigeon. The third animal died from absorption of toxin from the isolated loop after fourteen days. Postmortem examination of the third animal revealed a distended, intact, isolated loop with a hypertrophied wall. There was a serosanguineous transudate free in the abdominal cavity.

3. Loop Toxin and B. Welchii Toxin in the Veins of Dogs.—From 5 to 8 cc. of fluid from the isolated loops of two dogs were injected into the veins of three others. For two of these animals the toxic fluid from the loop of dog 38 of

section 1 was used. For one of these, a medium-sized dog, an equal quantity of the concentrated *B. welchii* antitoxin was mixed with 7.5 cc. of the loop fluid, allowed to stand a few minutes and then injected. The typical clinical and pathologic complex was observed in each of these dogs. The dog receiving the combined doses of *B. welchii* antitoxin and toxic loop fluid responded more quickly, clinically, to the intoxication than did the other two. From within a moment or two to within half an hour after injection the onset of these symptoms occurred in the three animals. There was dilation of the pupils, involuntary urination, marked retching and vomiting, diarrhea — extremely bloody in one case — hyperpnea and tremors and weakness of the posterior extremities. Coma intervened before death. The animals died in from one and a half to twelve hours after the injection. These symptoms were enumerated by Cooper [24] who thoroughly reviewed the recent literature dealing with intestinal obstruction.

At postmortem examination the lungs appeared collapsed and grossly normal. There was no evidence of hemolysis-staining of the lining of the heart or of the intima lining the larger blood vessels. About two thirds of the lining of the lower part of the duodenum, jejunum and ileum was blotched with petechial hemorrhages. The bowel content everywhere was red from bleeding.

TABLE 2.—*Data Pertaining to the Immunized Animals* *

Dog	Condition	Duration of Life, Days	Inhibition of Hemolysis on Titration of Serum	Extent of Protection of Pigeons by Serum, M. L. D.
70	Toxemia and peritonitis	2	Complete	1 cc. protects for 23 M. L. D.
71	Toxemia	14	Complete	1 cc. protects for 24 M. L. D.
83	Toxemia and peritonitis	9	Partial	1 cc. protects for 2.4 M. L. D.

* Complete and partial inhibition of hemolysis in the blood serum of these animals indicates the presence of some antihemolytic substance or substances. The protection of the pigeons against 1 M. L. D. or more of the toxin indicates the presence of immune bodies against the myotoxin.

Sufficient of the broth culture of *B welchii* (60 cc.) to contain 300 fatal doses for a pigeon was injected into the vein of another dog. A slight reaction occurred from this, such as a moderate diarrhea and retching. No such marked clinical symptoms occurred with the use of this toxin as when a very much smaller quantity of loop fluid was given. This difference was striking. The death of the animal occurred in twelve hours. On postmortem examination there were small areas of petechial hemorrhages of the lining of the lower part of the duodenum and of the jejunum and ileum. The bowel content was greenish brown. The blood in the cavities of the heart and large vessels was fluid, and the linings of these cavities were wine-colored from staining by hemolysed blood.

If the toxins of *B. welchii* were the lethal bodies of the loop fluid the *B. welchii* antitoxin should have neutralized them and delayed the response of the animal to the effects of the loop fluid. The *B. welchii* antitoxin gave no protection whatever. Dogs vary greatly in their response to the intravenous injection of fluid from occluded loops, some requiring large doses before death occurs. In those reported here, however, a much smaller quantity of the loop fluid than of the broth culture was required for fatal effects.

4. Effects of the Continued Absorption of Isolated Loop Fluid.—This report has to do with the three animals mentioned in section I from which the isolated

24. Cooper, H. S. F.: The Cause of Death in High Obstruction, Arch. Surg. **17**:918 (Dec.) 1928.

loops were removed before death occurred. One of them (no. 65) (table 3) was of the series that received 5 cc. of *B. welchii* antitoxin subcutaneously for eight days until the supply became exhausted temporarily. Its regular use was discontinued thereafter, and the animal had received no antitoxin for twelve days before the resection of the loop. There was progressive emaciation in spite of a heavy intake of food. For four or five days before the resection of the loop anorexia developed. This became so extreme that the dog could not be induced to take any food. The emaciation was extremely marked. On the twenty-sixth day after the isolation of the loop the abdomen was again entered under light ether anesthesia and the loop resected. Within a month after the resection of the loop the animal became well nourished again.

The length of the loop had increased from 35 to 78 cm., and its circumference was 12 cm. It contained 650 cc. of grayish-green fluid. The mucosa of the loop was everywhere intact, and the fibous and muscle tissue of the wall of the bowel was grossly thickened. The lumina of the blood vessels, particularly the veins, in the mesentery of the loop were from two to three times larger than they were when the loop was isolated.

The death of a pigeon occurred within eighteen hours after 10 mg. of the fluid from the loop was injected into the breast muscles. A strip of the muscle was removed aseptically and cultured anaerobically. There was a growth of gram-positive rods which produced a storm clot in milk mediums and which had the morphologic characteristics of *B. welchii*. The serum of blood removed from dog 65 at the time of the resection of the loop was kept at icebox temperature and was used in the attempt to protect pigeons from the lethal effects of the toxin of *B. welchii*. One cubic centimeter of the serum gave no protection for 1 minimal lethal dose. When one month had elapsed after the resection of the loop the animal was again bled and the blood serum was studied to see if it contained an antihemolysin. The method used was that described by Henry [25] for the neutralization of the toxin by the serum. Complete hemolysis occurred and there was no neutralization of the toxin by the blood serum.

Emaciation of the large hound (no. 38) occurred before the loop was resected on the forty-third day. This was 20 cm. in circumference, and it contained 750 cc. of thick, grumous, strawberry-colored fluid. The mucosa was intact; its blood vessels in the mesentery had increased from two to four times in size, and its length from 37 to 80 cm. There was a marked increase in the connective and muscle tissue in the wall of the loop. Cultures of the loop fluid grown anaerobically gave a growth of *B. welchii*. One cubic centimeter of the blood serum of this animal, removed when the loop was resected, did not prevent death in a pigeon when 1 minimal lethal dose of the toxin of *B. welchii* was given. Hemolysis was complete in the hemolysis tests. After the resection of the loop, the animal became well nourished within a month.

Animal 64 became very weak and emaciated in two weeks and died the day after the loop was resected. The loop was short and distended by 100 cc. of tarry, grumous material; its mucosa was intact, and the wall greatly thickened by fibrous tissue. *B. welchii* was isolated from fluid in it. No evidence of immune bodies against the myotoxin or the hemolysin of *B. welchii* was found in the blood serum of this animal by the pigeon and hemolysis tests similar to those described.

5. Tests for the Hemolysins of B. Welchii in the Portal Serum, Transudate and Chyle in Obstruction.—The hypothesis that the toxin of *B. welchii* is the

25. Henry (footnote 18, first reference).

toxic agent in the toxemia of acute intestinal obstruction would be materially strengthened if its presence in the abdominal transudate, the lymph from the thoracic duct or the portal blood serum of the animal with obstruction was demonstrable. This toxin is particularly suited for such studies for two reasons: If recovered in lethal quantities its antitoxin can be used to protect animals against its fatal effects, and it modifies the serums of animals so that they inhibit hemolysis.

Schönbauer [26] showed that the peritoneal transudate found with an obstructed bowel is toxic on intravenous injection into other animals. Stone and Firor [27] described experiments in which they demonstrated the toxicity of Ringer's fluid which had bathed an inflated loop of intestine containing fluid removed from another loop of obstructed bowel. The loop had been removed from the animal and it was deprived of all its blood supply. The conditions in experimental animals were not closely simulated by this experiment. Murphy and Brooks [2] collected the chyle from the thoracic duct of a dog a loop of whose bowel was isolated and contained fluid removed from the loop of another animal that had died from obstruction. The veins draining the loop were ligated. The fluid collected from

TABLE 3.—*Data Pertaining to the Serum of the Animals Having the Resected Loops* *

Dog	Date of Isolation of Loop	Date of Resection of Loop	Serum Collected	Inhibition of Hemolysis on Titration	Protection of Pigeons by by Serum
65	Aug. 10	Sept. 5	Sept. 5	.....	1 cc. gives no protection for 1 M. L. D.
			Oct. 6	Not increased	
			Oct. 20	Not increased	
38	Aug. 21	Oct. 3	Oct. 3	.....	1 cc. gives no protection for 1 M. L. D.
			Oct. 13	Not increased	
64	Jan. 21	Feb. 6	Feb. 6	Not increased	1 cc. gives no protection for 1 M. L. D.

* No increase of inhibition of hemolysis indicates the absence of antihemotoxin in the serum of these animals. No protection of pigeons for 1 minimal lethal dose of toxin denotes the absence in the serum of immune bodies against the myotoxin.

the thoracic duct produced death when injected into a small dog. In another experiment these workers increased the pressure in the closed loop containing toxic loop fluid removed from an animal with obstruction. A pressure of 48 inches of water was maintained. The veins draining this loop were not ligated. The chyle was collected and injected into the vein of another animal. Lethal effects were not produced.

Normal intestinal mucosa is impervious to lethal doses of the toxins of acute intestinal obstruction. Murphy and Brooks [2] felt that the factors that make the absorption of toxin possible were more important than the factors producing the toxin. They emphasized that the toxic materials are not rapidly absorbed through normal mucosa. The theory that increased intra-intestinal pressure is the factor that produces mucosal injury so that the toxins are absorbed in lethal quantities, stated most clearly by Murphy and Brooks,[2] has been stressed by Hartwell and

26. Schönbauer, L.: Die Fermente in ihrer Beziehung zu gewissen Erkrankungen der Gallenblase und zum Ileus, Arch. f. klin. Chir. **130**:427, 1924, quoted by Scholefield (footnote 14).

27. Stone, H., and Firor, W. M.: Absorption in Intestinal Obstruction: Intra-intestinal Pressure as a Factor, Tr. South. Surg. & Gynec. A. **37**:173, 1924.

his associates,[28] Dragstedt and his co-workers,[29] Scholefield,[14] Gatch, Trusler and Ayers[30] and by Morton,[31] who recently reviewed and contributed to this phase of the question. The distention of the intestine produced by the gaseous or fluid pressure injures the mucosa by occluding its blood supply.

When I was working as an assistant of Dr. Le Count at Rush Medical College, he repeatedly pointed out to me that the necrosis in human bodies is first evident in the epithelial covering of the tips of the valvulae conniventes squarely opposite the mesenteric attachment, that is to say, at the most peripheral point in the circulation of the blood in the bowel. When the protective layer of intestinal epithelium has been functionally destroyed, absorption takes place as from the peritoneal cavity the serosa of which exerts no physiologic selective action. Gross changes are usually always seen in the mucosa, but there is no reason to believe that even in the absence of any gross or histologic changes its physiology is not profoundly affected.

When the fluid from isolated loops is filtered through a Berkefeld filter much of the lethal substance does not appear in the filtrate. Moreover, the process of filtration is difficult if heat-labile toxins such as those of *B. welchii* are to be preserved. In this experiment it was the intention to allow the wall of the bowel to serve the function of the Berkefeld filter. Long loops of bowel were isolated, and the toxic fluids were placed in them and held at a pressure a little less than the diastolic blood pressure. This pressure was produced for the purpose of damaging the mucosa, physiologically if not grossly, in order that rapid absorption would occur. The abdominal transudate and the chyle and blood from the portal vein were recovered. The animals were kept under light ether or light sodium *iso*-amylethylbarbiturate anesthesia during the course of the experiments. Fluids were supplied subcutaneously in the form of normal physiologic solution of sodium chloride.

McIver and his associates[12] measured a pressure of 54 mm. of mercury in the unruptured isolated loops in dogs. Owings, McIntosh, Stone and Weinberg[32] reported that in obstructed loops of jejunum the pressure was from 30 to 45 cm. of water. Stone and Firor[27] found that the normal intra-intestinal pressure was 1.5 cm. of water, whereas the pressure above an obstruction was 150 cm. of water. In the present experiment a pressure of 60 mm. of mercury (corresponding to 81.6 cm. of water) was maintained in these long closed loops by means of either air or fluid. A Luer syringe, a mercury air valve and a mercury manometer were used to keep a constant head of pressure.

Murphy and Vincent[1] stated that the height of intoxication is apparently reached in from four to six hours when the mesenteric veins draining an occluded

28. Hartwell, J. A.; Hoguet, J. P., and Beekman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701 (May) 1914.

29. Dragstedt, Dragstedt, McClintock and Chase (footnote 6). Dragstedt, Moorhead and Burcky (footnote 4).

30. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Acute Intestinal Obstruction; Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173**:649, 1927; Causes of Death in Acute Intestinal Obstruction, Clinical Applications and General Principles of Treatment, Surg. Gynec. Obst. **46**:332 (March) 1928.

31. Morton, John J.: The Differences Between High and Low Intestinal Obstruction in the Dog, Arch. Surg. **18**:1119 (March) 1929.

32. Owings, J. C.; McIntosh, C. A.; Stone, H. B., and Weinberg, J. A.: Intra-Intestinal Pressure in Obstruction, Arch. Surg. **17**:507 (Sept.) 1928.

loop of bowel are ligated. In the experiments reported here the animals were found to fail rapidly when the intra-intestinal pressure with toxic fluids in the loop had been maintained for five or six hours. After the pressure had been maintained for five or six hours, sudden death occurred in some animals with so little warning that no time was given for the aspiration of the blood in the portal vein. In control experiments, when normal physiologic solution of sodium chloride was held under pressure in the loop, in place of the loop fluid, continuously for twelve hours or more, the animal lived for over twenty-four hours. This control was repeated in three instances with similar results.

TABLE 4.—*The Titrations for Antihemotoxin* *

Rabbit	Date	Amount, Cc.	Serum Collected	Inhibition of Hemolysis
1. Injected with transudate from dog 17	Oct. 6	1.5	Oct. 6	Normal
	Oct. 7	1.5	Nov. 25	Not increased
	Oct. 8	1.5	Dec. 23	Not increased
	Oct. 9	1.5		
	Oct. 10	1.5		
2. Injected with portal serum from dog 17	Oct. 6	1.5	Oct. 6	Normal
	Oct. 7	1.5	Nov. 25	Not increased
	Oct. 8	1.5	Dec. 25	Not increased
	Oct. 9	1.5		
	Oct. 10	1.5		
3. Injected with 24 hour broth culture of B. welchii	Oct. 6	1.5	Oct. 6	Normal
	Oct. 7	1.5	Nov. 25	Complete
	Oct. 8	1.5		
	Oct. 9	1.5		
	Oct. 10	1.5		
4. Injected with chyle from dog 24	Oct. 23	1.5	Oct. 23	Normal
	Oct. 24	1.5	Nov. 25	Complete
	Oct. 25	1.5	Dec. 23	Complete
	Oct. 26	1.5		
	Oct. 27	1.5		
5. Injected with transudate from dog 24	Oct. 23	4.0	Oct. 23	Normal
	Oct. 24	4.0	Nov. 25	Partial
	Oct. 25	4.0	Dec. 23	Complete
	Oct. 26	4.0		
	Oct. 27	4.0		

* The transudate and serum of the blood from the mesenteric veins of the loop containing loop toxin contained no hemotoxin. The transudate and the chyle from the loop containing the toxin of B. welchii contained toxin in sublethal quantities. This produced the antihemolysins in rabbits 4 and 5.

Loop fluid and broth cultures of *B. welchii* were held under pressure, and the transudate, chyle and blood from the mesenteric veins were collected. These were immediately injected into pigeons and into mice. No constant effects of their toxicity were found.

The following experiment was then carried out to determine the presence of sublethal quantities of the toxin of *B. welchii* in the portal blood serum and abdominal transudate. With the animal (dog 17) under sodium *iso*-amylethylbarbiturate anesthesia, almost the entire small bowel was isolated by the Parker-Kerr method. The distal end was closed, and a rubber tube was fixed into the proximal end by purse-string sutures. Seven hundred fifty cubic centimeters of loop fluid removed from the loop resected from dog 38, mentioned in section 4, was introduced into this long isolated loop, and the abdomen was closed. The pressure in the loop was raised to 60 mm. of mercury and held at this level. After five hours, when it became evident that the animal was failing rapidly, the abdominal

cavity was again opened, and 250 cc. of portal blood was aspirated from the radicles of the portal vein draining the loop. A similar quantity of serosanguineous transudate was also removed from the abdominal cavity.

The blood and the transudate were kept at icebox temperatures, and contact with the air was prevented by an oil seal. Into the veins of a rabbit, 1.5 cc. of this blood serum was injected for five successive days. In a similar manner a second rabbit was inoculated with doses of the transudate. After five weeks hemolysis was unaffected by the serums of these rabbits (table 4).

A control experiment was performed. Under light ether anesthesia almost the entire small bowel of dog 24 was isolated. A rubber tube, secured by purse-string sutures, was placed in the proximal end. The greatest care was used to prevent leakage into the peritoneal cavity. Three hundred cubic centimeters of the broth culture of *B. welchii*, containing 1,500 minimum lethal doses for a 350 Gm. pigeon, was placed in the loop. An intra-intestinal pressure of 60 mm. of mercury was held for six hours. The thoracic duct was cannulated at the beginning of the experiment and the chyle was collected. The chyle became pink from blood as soon as the pressure was raised in the isolated loop of bowel. When the life of the animal was seen to be ebbing, the abdomen was reopened. It died before aspiration of the blood from the portal vein could be done. The serosanguineous transudate was removed from the abdominal cavity and used to inoculate a rabbit by five intravenous doses of 4 cc. each. A second rabbit received intravenously five doses of 1.5 cc. each of the chyle. A third rabbit was given five doses of 1.5 cc. each of a portion of the culture of *B. welchii* that was used in the isolated loop in this experiment. After five weeks the three rabbits were bled, and the ability of their serum to inhibit hemolysis was examined. The serums of the rabbits that received the chyle and the transudate gave as good protection against hemolysis as that of the rabbit which received the pure culture. In all of these experiments the rabbits were bled before inoculation, and the content of antihemolysins of their serums was measured. None existed in any of them.

COMMENT

After isolation of short loops of the proximal part of the jejunum in dogs death occurs as a rule in from two to five days after continuity of the gut is reestablished. The production of a closed loop is a questionable procedure because rupture of the loop with peritonitis is so commonly found after death, to which, of course no immunity is possible. If the loop is intact and if on postmortem examination no other cause for death is found, it is reasonable to assume that absorption of some of the lethal bodies within the loop has caused death. As evidence that dehydration did not occur in such animals, reported in sections 1 and 2 of this study, a clear serosanguineous transudate was found free in the peritoneal cavity. In the animals with unruptured loops and without simple obstruction the administration of the specific antitoxin should have prolonged life if the absorption of that particular toxin is the cause of death. The control animals that died from toxemia lived on the average 1.4 days longer than did the animals with a similar condition that received daily injections of 5 cc. of the concentrated *B. welchii* antitoxin (table 1). The antitoxin had neither a prophylactic

nor a therapeutic value, for life in the protected series should have been prolonged. Similar results were obtained by Owings and McIntosh.[33]

Dogs may be immunized to the toxins of *B. welchii*, but there are variations in their response to inoculations with these toxins. Bull and Pritchett [34] found that one prophylactic dose of *B. welchii* antitoxin furnished protection to a guinea-pig for twelve days when given the day before the infection occurred. Active immunization did not protect these animals against the toxins absorbed from the isolated loops (table 2).

While not pertinent to this study, it is an interesting observation that in all of the animals reported in section 1 in which simple obstruction occurred along with the isolation of the loop not one of the loops was ruptured. Some of the loops were flabby and relaxed, and their content was pasty. There was no connective tissue or muscle hypertrophy in the walls of these loops. Braeye [35] found that there was a latent period of ten to twenty hours in animals before the pressure in the loop was sufficient to cause necrosis and perforation. Thirty-six hours were required for toxic properties to develop in the loop fluid. In the animals with simple obstruction, mentioned in section 1, the secretion-absorption ratio within the loop was disturbed by the dehydration effects of the simple obstruction which evidently started before the end of this latent period, and therefore overdistention of the loop did not occur. Such animals [5] lived for an average of 13.2 days. Death was due to dehydration and starvation. If the usual lethal products of obstruction were in the loops, they were not absorbed in sufficient quantity to cause an early death. The mucosa had exerted a selective absorption of fluids, however, for the loop content in some was thick and pasty.

Dragstedt [6] noted that if loops 25 cm. and longer are isolated, rupture of the loop does not always occur, but the animal will die in a few weeks because the liver is not able to cope with the toxic substances absorbed. The animals described in section 4 from which the loops were resected were overwhelmed by the continued absorption of the toxins of the loop content. *B. welchii* was grown from each loop. It is to be expected that animals suffering from a toxemia caused by intestinal obstruction would show a marked immunity to the toxin of *B. welchii* if that is the toxin absorbed. The toxemia of these animals was not due to the toxins of *B. welchii*, because no specific immune bodies were produced in their serums.

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33. Owings, J. C., and McIntosh, C. A.: Perfringens Antitoxin and Experimental Intestinal Obstruction, Arch. Surg. **18**:2237 (June) 1929.

34. Bull and Pritchett (footnote 17, second reference).

35. Braeye, L.: On the Formation of the Toxic Fluid Found in Isolated Duodeno-Jejunal Loops, Bull. Johns Hopkins Hosp. **39**:121, 1926.

In each of these resected loops there was a marked thickening of the connective tissue and muscular elements in their walls. This is evidence of the increased pressure within the loop. Furthermore, if the pressure within the loop had not been increased, no elongation or dilation of the loop would have occurred. The mucosa was not grossly injured, but its physiologic function was impaired for absorption of the lethal substances of the loop content had occurred, producing the gradual intoxication of the animals.

Because the toxin of *B. welchii* has a powerful effect on muscle tissue, Williams [8] expressed the opinion that the paralysis of the intestine in paralytic ileus might be due in part to the toxin of *B. welchii* in the contents to which the intestinal wall is exposed in greatest concentration. The attractiveness of this idea is enhanced by the studies of Buttle and Trevan.[36] They noted the effect of the toxin of *B. welchii* on strips of the isolated small intestine of the rabbit, suspended in a bath containing 15 cc. of Ringer's solution at 37 C. through which air or oxygen were bubbled. Spontaneous movements of the strips of muscle occurred. The addition of the toxin of *B. welchii* in sufficient amounts to the Ringer's solution in the bath caused a spasmodic contraction of the muscle. Then a diminution in the size of the spontaneous contractions occurred until they completely ceased. The previous addition of the antitoxin to the bath prevented the effect of the toxin. There is nothing in these studies to indicate that a sufficient quantity of the toxin of *B. welchii* is present to produce a similar reaction in the obstructed bowel.

CONCLUSIONS

1. Dogs suffering from a toxemia caused by acute intestinal obstruction are not helped by passive or active immunization to the toxins of *B. welchii.*

2. Dogs with acute intestinal obstruction produce no immune bodies for such toxins.

3. There is no evidence of the presence of the toxin of *B. welchii* in the abdominal transudate or in serums of blood from the mesenteric veins of dogs with acute intestinal obstruction.

4. A method is suggested whereby the toxin of *B. welchii* may be used for experimental studies of the routes of absorption of toxins from obstructed portions of the bowel.

5. There is no direct or indirect evidence that toxins of *B. welchii* have any rôle in the toxemia of acute intestinal obstruction.

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36. Buttle, G. A. H., and Trevan, J. W.: The Action of Vibrion Septique and B. Welchii Toxin on Isolated Organs, Brit. J. Exper. Path. **9**:182, 1928.

CONTINUOUS INTRAVENOUS INJECTION OF DEXTROSE IN RINGER'S SOLUTION

ITS TECHNIC AND INDICATIONS, AND A NEW INTRAVENOUS CANNULA *

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In certain cases the advantages of supplying by other than the oral route not only water and the electrolytes of the blood, but caloric values, have become more and more obvious. Various modes of doing this have been much discussed.[1] Under conditions approximately normal, the administration of food, water and the necessary salts by mouth is sufficient, but in many diseases, and particularly in surgical cases, this route alone is unsatisfactory, either because the stomach and intestines will not absorb a sufficient amount of nutrition and water, or because physiologic rest of these organs is indicated.

McNealy [2] and McNealy and Willems [3] have shown that dextrose is apparently not absorbed by the colon, though salt solution is taken up more rapidly by the colon than by the ileum. They believe that the dextrose in enemas of dextrose solution is absorbed only if the ileocecal valve is incompetent and the dextrose is forced into the ileum, which doubtless sometimes occurs. A concentrated solution of dextrose as an enema is irritating, and even the isotonic 5 per cent solution may be broken down into irritating products by the bacteria in the colon.

Matas,[4] in 1924, advocated the use of what he called a "continuous intravenous drip," giving 5 per cent solution of dextrose in distilled water into a vein over a period of several days.

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* Submitted for publication, June 9, 1930.

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1. Horsley, J. Shelton: The Influence of Physiologic Research on Modern Surgery, Virginia M. Monthly **55**:790, 1929; The Intravenous Administration of Dextrose in Ringer's Solution, J. Tennessee M. A. **23**:169, 1930.

2. McNealy, R. W.: Personal communication, Feb. 8, 1930.

3. McNealy, R. W., and Willems, J. D.: The Absorption of Glucose from the Colon, Surg. Gynec. Obst. **49**:794, 1929.

4. Matas, R.: Continued Intravenous "Drip," with Remarks on the Value of Continued Gastric Drainage and Irrigation by Nasal Intubation with Gastro-Duodenal Tube (Jute) in Surgical Practice, Ann. Surg. **79**:643, 1924.

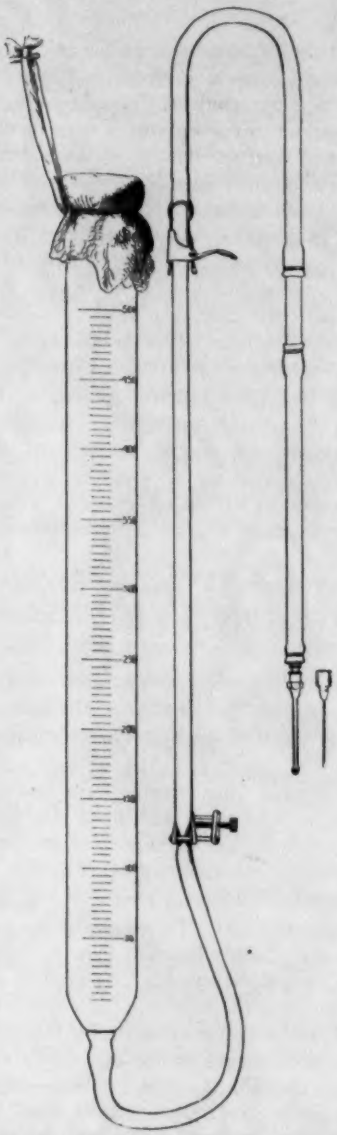

Fig. 1.—The buret, tube, thumb screw clamp, spring clamp, metal nipple, cannula and hypodermic needle, assembled for intravenous administration of dextrose in Ringer's solution. The cannula is the only thing in the group that is original. A glass tube connection is placed at the end of the long rubber tube connecting it with a shorter segment of rubber tube. In this way it can be observed whether blood is flowing back into the rubber tube or whether there are air bubbles, and in the short segment of tube the nipple is tied.

TECHNIC

Adopting the method of Matas as a principle, we have modified the technic somewhat by using a buret 54 cm. long in which 100 cc. of fluid is contained in 9.2 cm. of the length of the buret (fig. 1). The flow can be regulated by a screw clamp from 75 cc. an hour up to as much as it may be necessary to give quickly when shock occurs. In this way the danger of the entrance of air into the vein is largely obviated, while a constant rate of flow is maintained.

The rubber tubing should be boiled, stretched and twisted or beaten before and after being boiled, and sterile water run through it, in order to remove deposits that may cause a reaction. New rubber tubing is boiled for an hour in strong solution of soda, rinsed in running water and then boiled for an hour in tap water. At the end of the tube is a small connecting tip or metal adapter (or nipple) which fits into the hypodermic needle of a Luer syringe. A glass tube is inserted near the end of the rubber tube (fig. 1).

All glass used in preparing the solution is pyrex, and new glass is thoroughly washed before using.

To the 5 per cent isotonic solution of dextrose of Matas, we add Ringer's solution. After two days the vein becomes tender, and usually by that time the patient has had sufficient amount of the solution for immediate needs. It is best, then, after two or three days, to remove the intravenous cannula and give the

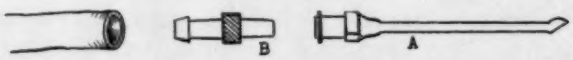

Fig. 2.—*A* shows the intravenous cannula. Note the oblique opening at the tip, which makes it easy to insert. *B* is the metal nipple or adjuster that is tied in the tube and fits into the base of the cannula or hypodermic needle.

patient a rest for a day or two, when another vein may be utilized if necessary. In patients with large, accessible veins, and when the indications for giving the solution are for not more than ten or twelve hours, a hypodermic needle is satisfactory for the intravenous administration. For this we use a no. 20 gage, stainless steel needle, 1½ inches (3.7 cm.) long.

We have devised a cannula which is employed when the solution is to be given for more than ten or twelve hours. This cannula measures 5.6 cm. in length and has at its tip an oblique opening that permits it to be introduced into the vein as easily as a grooved director (fig. 2). Its lumen is large and clear throughout, which lessens the chances of its being stopped up. The base of the cannula is ground to fit an ordinary Luer syringe, so by merely disconnecting the metal adapter or nipple on the tube through which the intravenous solution flows the cannula is at once available for transfusion of blood by the syringe method. After the transfusion, the adapter may again be inserted into the cannula, and the dextrose and Ringer's solution can be continued.

The advantages of Ringer's solution were demonstrated by Ringer himself when he first used physiologic solution of sodium chloride for maintaining the isolated heart of a frog or a turtle and found that after this solution had become almost ineffective the addition of a small amount of calcium would cause marked contraction. Ringer's solution contains 0.7 per cent sodium chloride, 0.03 per cent potassium chloride

and 0.025 per cent calcium chloride in distilled water. It has the mineral elements of the plasma of the blood (sodium chloride, potassium chloride and calcium) in approximately the same ratio as found in the blood serum. Potassium seems to cause a relaxation of the heart muscle and calcium contraction.

Calcium not only tends to stimulate the heart, but in such amounts as in Ringer's solution is not injurious to the subcutaneous tissues. In one patient in whom this solution was used, the needle slipped from the vein, and there was a considerable amount of infiltration in the tissues of the forearm; but on withdrawing the needle the solution was readily absorbed without any ill effects. Ringer's solution may be employed for hypodermoclysis. Of course, greater concentrations of calcium are very irritating to subcutaneous tissues. If there is an indication for increasing the calcium in the blood, as in slow clotting or in jaundice, additional calcium may be injected with a hypodermic syringe into the tube while the dextrose and Ringer's solution are flowing. This is better than pouring it into the buret, for when injected it is quickly washed out of the vein.

Calcium also retards the passage of fluids from the vascular system by decreasing the permeability of the blood and lymph vessels.[5] If too strong, its effects in this respect may be deleterious, particularly to the function of the kidneys; but in the strength in Ringer's solution, this tendency of calcium to hold the solution in the vascular system is helpful in shock, aside from the stimulating effect of calcium on the heart.

Five per cent dextrose is approximately an isotonic solution, and while this can usually be utilized by the tissues, it is advisable in a weakened patient to add some insulin, about half of the amount necessary for the complete conversion of the dextrose. We inject into the tube 10 units of insulin for every 500 cc. of dextrose in Ringer's solution as the solution is flowing. The use of insulin with dextrose solution given intravenously has been advocated by Ort,[6] Thalhimer,[7] Fisher and Snell,[8] Andrews and Reuterskiold,[9] and others.

Dextrose found on the market in bulk is not chemically pure. While it may be labeled "chemically pure quality," a glance at the printed analysis will show some impurities that may cause a reaction. The

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5. Sollmann, Torald: A Manual of Pharmacology, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 795.

6. Ort, M.: Treatment of Post-Operative Acidosis by Means of Insulin, Arch. franco-belges de chir. **27**:994, 1924.

7. Thalhimer, W.: Insulin Treatment of Postoperative (Nondiabetic) Acidosis, J. A. M. A. **81**:383 (Aug. 4) 1923.

8. Fisher, D., and Snell, F.: The Insulin Treatment of Preoperative and Postoperative Nondiabetic Acidosis, J. A. M. A. **82**:699 (March 1) 1924.

9. Andrews, Edmund; and Reuterskiold, Knute: Dangers in the Postoperative Use of Insulin, Surg. Gynec. Obst. **47**:665, 1928.

dextrose solution in ampules seems to be purified to such an extent that it is much less likely to cause a reaction.

Ringer's solution may be made from tablets and freshly distilled water, and the dextrose added later. However, we have had prepared an ampule which is much more convenient and the purity of which seems to be satisfactory. The ampule contains 100 cc. of a solution of dextrose and Ringer's solution in such a concentration that when added to 400 cc. of freshly distilled water a solution of 500 cc. of 5 per cent dextrose and normal Ringer's solution results. The contents of an ampule are poured into a flask, 400 cc. of freshly distilled water is added, the flask is shaken, and the solution is ready for use. In whatever way the solution is prepared, freshly distilled water—certainly not more than twenty-four hours old—should be used.

Precautions as for any intravenous administration should be taken in expelling the air as far as possible from the tube. If a hypodermic needle is used, it is introduced attached to a syringe, which is half filled with physiologic solution of sodium chloride, and when blood is drawn back freely into the syringe, showing that the needle is in the vein, the constriction on the arm is released, the needle is strapped in position with adhesive plaster, the syringe is detached, and the connecting nipple in the rubber tube from the buret is attached to the hypodermic needle with the solution flowing. When the cannula is used, a short incision, usually transverse, is made over one of the large veins just below the bend of the elbow, and the cannula is inserted in the usual manner. It may be inserted while connected with a syringe, as with the hypodermic needle, though this is not essential; it would prevent, however, reflux of blood into the cannula if the clamp on the vein should become displaced, and so render clotting in the cannula less likely to occur.

It is important to see that there is a constant flow through the cannula. If it becomes plugged, the flow may sometimes be reestablished by elevation of the buret, which increases the pressure; if this does not open the cannula, the connecting nipple is detached and the clot loosened with a probe and sucked out with a syringe. If the obstruction is due to clotting in the vein, the cannula should be removed and inserted elsewhere.

We now use the ampule of prepared concentrated dextrose and Ringer's solution, but of course, the Ringer's solution may be made separately and an ampule of dextrose added later, or the Ringer's solution may be used alone if there is a contraindication for dextrose, as in diabetic patients. If tablets for Ringer's solution are used, a sufficient amount is thoroughly dissolved in 50 cc. of distilled water, and this solution is filtered through three thicknesses of fine white silk

cloth, using glass funnels only. New cloth is always thoroughly washed before using. The 50 cc. of solution is added to 1,950 cc. of distilled water, making 2,000 cc., which is boiled slowly for ten or fifteen minutes. The solution is dated and should not be used if over twenty-four hours old.

The rate of flow is regulated by a thumb screw clamp. Hot water bottles are hung around the buret and over the tube, though it is probably not so important to maintain accurately the temperature of the solution as was formerly thought. The small amount of fluid entering the body cannot affect its temperature greatly if there is a variation of only a few degrees.

For patients who are edematous or whose renal function is greatly impaired, salts should not be used. In such instances, 5 per cent dextrose alone may be administered. When the function of the kidneys is markedly affected, the strength of the dextrose can be increased to 10, 15 or 20 per cent. The giving of a very concentrated dextrose solution, however, may not be entirely without danger. Certainly it causes a marked irritation of the vein and draws fluid rapidly from the tissues. Higher concentrations, such as 20 per cent or more, should be given rather quickly.

The rate at which the intravenous flow of dextrose and Ringer's solution should be maintained depends entirely on the conditions. In hemorrhage or shock, it should be rapid enough to secure almost a normal blood pressure within a short time. In shock, when the blood pressure is low, it is impossible to overload the heart until the blood pressure has approximated what is normal for that individual. The lumen of the cannula will permit a rapid flow, and as much as 400 or 500 cc. of the fluid can be given in a few minutes, until the blood pressure is within ten or fifteen points of the patient's normal pressure; then it is cut down to a rate of 150 or 200 cc. an hour and maintained until the clinical condition is satisfactory. When hemorrhage is marked or after shock has been well established, dextrose in Ringer's solution may not be entirely effective, but it can be utilized until a donor is secured for a transfusion of blood. It is much better for the patient to have the blood pressure kept up even temporarily by a solution that contains no abnormal constituents of the blood than to have a marked drop in blood pressure continue over some time with its subsequent deleterious effect on the brain, kidneys and vital organs.

For other conditions than shock or hemorrhage the solution should be given at a rate of from 75 to 200 cc. per hour.

When the hemoglobin is below 45 or 50 per cent, the oxygen-carrying power of the blood is greatly affected, and even though dextrose in Ringer's solution is beneficial, it would doubtless be better to give a transfusion of blood and then continue the solution.

In spinal anesthesia there is often a marked drop in blood pressure. We make a practice of beginning intravenous injection of dextrose in Ringer's solution immediately after the spinal anesthesia, and before the operation is commenced. Either a needle or a cannula can be used, depending on the conditions. If it is to be a long operation, particularly if it is resection of the stomach with the indications for supplying nutrition, water and the electrolytes for some days, or if there is the possibility of the needle becoming obstructed, a cannula is inserted. If the blood pressure begins to fall, the clamp on the tube is opened widely and a small amount of epinephrine solution is injected into the tube with a hypodermic syringe while the solution is running. This will quickly bring the blood pressure up several points, where it can usually be maintained.

When there is much vomiting, as in intestinal obstruction, the dextrose and Ringer's solution should be given, and an additional amount of sodium chloride may be added as recommended by Haden and Orr.[10]

In the loss of pancreatic juice, as with a duodenal fistula, or in obstructive vomiting when the pancreatic juice is regurgitated into the stomach, this solution is very effective. In malnutrition or after operations in which it is desirable to give rest for the stomach and intestinal tract, the continuous administration of dextrose and Ringer's solution is indicated. In the vomiting of pregnancy it is beneficial. In peritonitis and sepsis, it is very satisfactory. In diarrhea and dysentery, when there is marked dehydration, it is excellent. In toxic goiter and hyperthyroidism, it acts as a buffer for the tissues that are burned up by the increased metabolism, and in this way the tissues are protected from excessive oxidation; so it is indicated after operations for hyperthyroidism.

One gram of dextrose equals 3.75 calories, so in giving 3,600 cc. of a 5 per cent solution of dextrose in twenty-four hours, at the rate of 150 cc. an hour, we supply 675 calories. It is obvious that this puts the patient in a better condition, even though the calories are not up to normal, than if he were not absorbing nutrition, or if it were attempted to force nutrition through the bowel, the function of which was impaired from weakness or from the operation.

In patients who are vomiting or who have fistulous openings or diarrhea, the discharge of body fluids is a kind of safety valve, and more of the solution may be given than if these conditions were not present. If the patient is thin and the blood pressure high, the solution should be used with caution. When large quantities of this or of any

10. Haden, R. L., and Orr, T. G.: Use of Sodium Chloride in the Treatment of Intestinal Obstruction, J. A. M. A. **82**:1515 (May 10) 1924.

intravenous solution are given for several days, "water sickness" sometimes appears. It comes on gradually, the early symptoms being puffiness of the lower eyelids, watering of the eyes and vomiting of clear or bile-stained fluid. Discontinuance of the solution is quickly followed by disappearance of the symptoms.

The administration of this dextrose and Ringer's solution often permits operations such as excision of the rectum to be done in one stage instead of in two or more. By keeping the solution flowing slowly and turning on more when the blood pressure becomes lower, the operation can usually be completed in one stage. The advantages of removing all of a cancer in one stage as a block dissection instead of in two stages are obvious. If at the end of the procedure the patient still shows symptoms of shock, a transfusion of blood can be done, and the dextrose and Ringer's solution can be continued.

We have practiced the general principles of the technic herein described for about six years, beginning soon after the publication of the paper by Matas.[4] It has been employed in about 750 cases. The reactions have been few, and in the past two years since using the purified dextrose in ampules there have been only three or four reactions that could be attributed to the intravenous injection, and these have not been followed by bad effects.

THE FATE OF THE CORTICAL BONE GRAFT*

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Although many tissues of the body are commonly transplanted and recognized to retain their viability and regenerative power, comparatively little is known of the histogenetic properties in transplanted bone.

The object of this series of experiments was an attempt to determine whether autoplastic cortical bone when grafted into cortical bone in its normal relationship becomes a living integral part of the skeleton or whether it simply acts as a temporary scaffold for the deposit of new bone cells that fills in the defect with new bone.

By microscopic examination alone it is impossible to determine whether the transplant has lived in bulk or whether it has died and served only as a framework for the deposit of new bone.

In botany, where plant life easily lends itself to this variety of experimentation, it is positively proved in tree grafting that the graft lives in bulk, grows and produces limb and fruit of the variety of the graft. Why should not a bone graft live and grow in the human skeleton in a similar manner?

For this series of experiments advantage was taken of the fact that in an animal fed on a diet containing sodium alizarin sulphonate (synthetic madder root dye) all new bone developed while the dye is being administered is colored "madder red," while the bone formed before the dye is given remains the natural color. This makes a striking distinction in the color of the bone developing from a definitely fixed time.

To get the control in color, two animals were used for each experiment. To have the transplantation as nearly autoplastic as possible, two pups from the same litter were used in each experiment.

The first pup was given a small amount of alizarin in its food, beginning as soon as it was weaned, so that its skeleton would be well

* Submitted for publication, April 28, 1930.

* From the Laboratories of the University of Illinois College of Medicine and the University Hospital.

* Read before the Medical Research Club of the University of Illinois, May 14, 1930.

* Read before the Chicago Surgical Society, April 4, 1930.

colored at the time of the transplantation of the graft. The dye was continued in its food after the transplantation of the graft until the animal was killed.

The second pup was given ordinary diet without dye, both before and after the transplantation of the graft.

The scheme of the investigation was as follows:

1. If on exposure of the area of transplantation on the living animal and removal of the periosteum under ether, the graft was demonstrable and oozed blood freely from its surface, then it evidently was living bone.

2. If in the dog the skeleton of which was dyed, an undyed transplant was grafted and the dyeing process continued for a period long enough for any metamorphosis in the graft to be completed, and on exposure of the graft it was found to have only a very faint tinge of pink, such as would be produced by the natural increase of new bone cells in a young dog, and if this graft was entirely surrounded by dark red bone, then evidently the graft as transplanted had practically become an integral part of the skeleton of its host.

3. Alizarin has the specific action of dyeing developing bone cells. When a bone cell reaches maturity, the dyeing process ceases, the cell becomes calcified, and the pigment is sealed in. The color remains permanent during the life of the bone cell. At the death of the bone cell the mineral salts are absorbed, the pigment is liberated and dissipated, and the color disappears. Therefore, if in the dog with an undyed skeleton a dyed transplant was grafted and no alizarin was given after transplantation, and the life of the animal was preserved for a sufficient length of time for any metamorphosis in the graft to be completed; and if on exposure of the graft, it was found to consist of dark red bone entirely surrounded by natural colored bone, evidently the graft colored as transplanted was living bone and had become an integral part of the skeleton of its host.

Throughout the experiments, only young healthy dogs were used, and all features of modern aseptic surgery were observed. The animals used were in the growing age, and transplantation was done only in those from the same litter.

EXPERIMENTAL PROCEDURE

The experimental procedure and histogenetic observations noted were as follows:

Experiment 1 (dog 1).—This dog was fed alizarin for sixty days. At this time a transplant from the cortical layer of the frontal bone, 1 by 2 cm., was removed and interchanged with similar bone from dog 2, which had received no alizarin in its diet. Alizarin was continued for 250 days after the initial operation; then the animal was operated on again.

It was anesthetized with ether, and the area of original operation exposed. All flesh and periosteum were removed.

The graft was apparent as an area of natural colored bone surrounded by dark red bone. There were minute bleeding points evenly distributed over the entire surface of the graft.

After observation of the graft and surrounding bone in the living dog, it was killed. The part of the skull containing the transplant was removed and immediately examined. It showed an inset of natural colored bone, of the size, shape and thickness of the transplant and, surrounded by dark red bone, grafted to the surrounding bone. The cortical bone at the edge of the graft and the cancellous bone underneath it were dyed dark red. There was a sharp line of distinction in color between the graft and the surrounding bone.

On close inspection of the cut surface of the transplant a very faint tinge of pink was seen, showing that there had been the natural growth of new bone cells in the graft after transplantation.

EXPERIMENT 1 (dog 2).—This dog received the regular diet without alizarin. A transplant from the cortical layer of the frontal bone, 1 by 2 cm., was removed and interchanged with similar bone from dog 1, which had received alizarin for sixty days prior to operation. The diet was continued as before operation. This dog was operated on again 254 days after the first operation. The dog was anesthetized with ether, and the area of original operation was exposed. All flesh and periosteum were removed.

The graft was apparent as a dark red area surrounded by natural colored bone. There were minute bleeding points evenly distributed over the entire surface of the graft.

After examination of the graft and surrounding bone in the living dog, it was killed. The part of the skull containing the transplant was removed and immediately examined. The graft was apparent as an inset of dark red bone, of the size, shape and thickness of the transplant, surrounded by bone of natural color. A cross-section of the transplant showed it to be well grafted to the surrounding bone. There was a sharp line of distinction in color between the graft and the surrounding bone.

EXPERIMENT 2 (dog 3).—This dog was given alizarin for seventy-two days. At the end of this period a transplant from the cortical layer of the frontal bone was removed and interchanged with bone of similar location and dimensions from dog 4, which had received no alizarin. The diet containing alizarin was continued for 249 days, when it was operated on and killed.

The observations at operation and examination of the specimen were in detail as those found in dog 1, in the previous experiment.

EXPERIMENT 2 (dog 4).—This dog was not given alizarin. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 3. The animal was operated on and killed after 249 days.

The observations at operation and examination of the specimen were in detail as those found in dog 2, in the previous experiment.

EXPERIMENT 3 (dog 5).—This dog was fed alizarin for eighty-three days. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 6, which had received no alizarin. The alizarin was continued for 300 days, after which the animal was operated on and killed.

The observations were in detail as those in dogs 1 and 3 in the previous experiments.

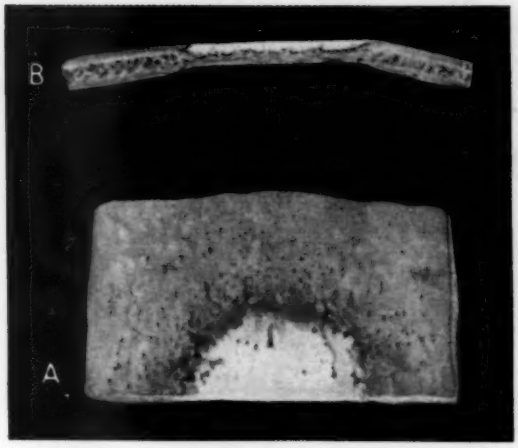

Fig. 1

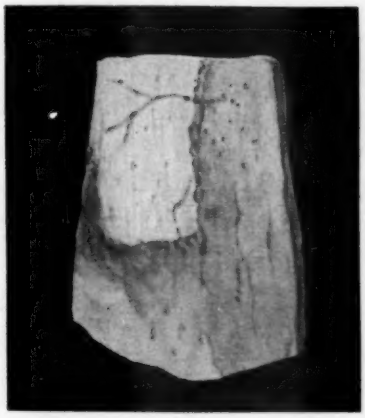

Fig. 2

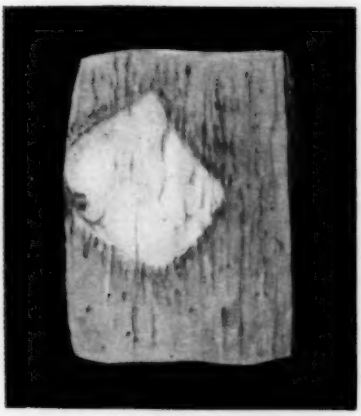

Fig. 3

Fig. 1 (dog 1).—*A* shows graft as an inset of bone of natural color in a field of dyed bone, after 250 days; *B*, a cross-section through the specimen.

Fig. 2 (dog 3).—Graft as an inset of bone of natural color in a field of dyed bone, after 249 days.

Fig. 3 (dog 5).—Graft as an inset of bone of natural color in a field of dyed bone, after 300 days.

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EXPERIMENT 3 (dog 6).—This dog was not given alizarin. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 5. The animal was operated on and killed after 300 days.

The observations at operation and examination of the specimen were in detail as those found in dogs 2 and 4 in the previous experiments.

SUMMARY

From this series of experiments it is our opinion that an autoplastic cortical bone graft transplanted aseptically into cortical bone with perfect mechanical adaptation and fixation will heal by primary intention, with preservation of the vitality of the graft.

VACCINATION AGAINST PERITONITIS IN SURGERY OF THE COLON

FURTHER REPORT *

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In December, 1928,[1] we reported before this association, sixty-one cases of tumor of the colon resected after the patients had had the benefit of cooperative management of a medical and a surgical service. Among the details of the treatment, intraperitoneal vaccination was considered one of the essentials. The striking reduction in mortality in this group over the control group, in which operation was performed by the same surgeons under the same circumstances, increased our belief that this was an important detail in guarding against the peritonitis which is the customary cause of death in more than half of these cases.

Our efforts to ascertain more closely the merits of intraperitoneal vaccination, as applied clinically, were stimulated by the experimental work of Herrmann[2] in 1928. We carried this work forward and by Oct. 1, 1929, we had increased to 300 the series of cases in which vaccination and operation had been done. In addition, we have been able to correlate some experimental results obtained by Kellum[3] working in Rosenow's laboratory, which suggest that the introduction of a mixed vaccine of colon bacilli and streptococci has a very important bearing on mortality statistics by increasing the immunity to infection and thus raising the threshold of surgical safety.

Peritoneal contamination has always been considered one of the most serious menaces to successful surgical treatment of the colon, and any agent which obviates peritonitis or militates against it is a highly desirable adjunct to the surgeon's armamentarium. It is evident that vaccine, as a single step, probably would fail to accomplish satisfactory

* Submitted for publication, Jan. 20, 1930.

* Read before the Southern Surgical Association, Atlanta, Ga., Dec. 10, 1929.

* From the Division of Surgery and Division of Medicine, the Mayo Clinic.

1. Rankin, F. W., and Bargen, J. A.: Carcinoma of the Colon: Intraperitoneal Vaccination by Mixed Vaccine of Colon Bacilli and Streptococci, Arch. Surg. **19**: 906 (Nov.) 1929.

2. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, Arch. Surg. **18**: 2202 (May) 1929.

3. Kellum, E. L.: Unpublished data.

results, and that it must be combined with other cooperative measures. The reasons for peritonitis developing so frequently group themselves mainly under three headings: (1) the peculiar conformation of the large bowel, which differs from the small intestine anatomically and physiologically; (2) the increased permeability of the large bowel when attacked by malignant disease, due either to its peculiar structure or to mucosal injury produced by large ulcerating carcinomas, and (3) the general condition of the patient as evidenced by the debilitated, dehydrated and generally lowered resistance of patients who harbor neoplasms.

The anatomic construction of the large and the small intestinal canals differs considerably, and thereby, in technical maneuvers on the large bowel, influences are brought to bear which do not pertain to the upper part of the gastro-intestinal tract. The musculature of the large bowel is markedly thinner than that of the small intestine, and the tunica propria, which is beneath the endothelial layer and which contains lymphatic channels as well as blood vessels, is frequently replaced by fat. The powerful peristaltic action of the large bowel, which normally is greater than that of the small intestine, likewise increases the strain on suture lines, with occasional concomitant leakage and abscess formation or peritonitis. The inconstant blood supply of the large bowel, and the occasionally independable anastomosis between the arcs, likewise is sometimes a factor in causing a spot of lowered resistance which may result in contamination. These anatomic factors, plus the increased permeability of the large bowel under obstructive conditions, bear a direct relation to contamination. Given a slow, encroaching growth which encircles the lumen of the large bowel and stenoses it gradually, one finds increased peristalsis as the resistance progresses, and a greater attempt on the part of the intestine to empty itself. If this occurs in the presence of an ulcerating and fungating neoplasm, the infection is much more readily spread to the adjacent tissues and is indeed demonstrable in peritoneal tissues at a considerable distance from the original growth. The mucosal injury and the stenosis at the site of the growth are the two factors which increase permeability and spread contamination. Neither factor alone is sufficient, but the combination, as it is usually found in cases of malignant growths of the colon, is a constant and necessary factor in subsequent infections. We have a fixed idea that manipulation of colonic growths with spreading of the peritoneal infection already present, is a greater source of potential danger than leakage at the suture line or other technical factors which so often are blamed for failures in operations.

Recently we have made cultures from eighteen malignant colonic lesions immediately after their extirpation, and the results obtained seem

to bear out the assertions made relative to the infection in the peritoneal tissues in immediate juxtaposition to the growth. The tumor was removed by surgical resection under the strictest aseptic precautions; the peritoneal surface was immediately seared with a hot spatula after the usual method of searing tissues for culture. A sterile Pasteur pipet was inserted just under the serosa of the tumor and another just into the outer edge of the tumor; material was aspirated and immediately transferred to dextrose-brain broth (Rosenow's medium) and shake cultures were made with blood agar. The lesions of the bowel from which cultures were made included carcinomas of the cecum, ascending colon, hepatic flexure, splenic flexure, descending colon, rectosigmoid and rectum. In cultures of thirteen lesions, only short-chained, green-producing streptococci and colon bacilli grew; in cultures of three lesions, no bacteria grew; in cultures of one lesion only, gram-negative bacilli resembling colon bacilli grew, and in another, staphylococci, and gram-negative and large gram-positive bacilli grew. Thus, it is seen that in 72 per cent of the lesions cultured, only green-producing streptococci and colon bacilli grew, in 17 per cent no bacteria grew, and cultures of the other 11 per cent were indeterminate. This would certainly suggest that the vastly predominating bacteria in and around malignant lesions of the colon are streptococci and colon bacilli.

That the visceral peritoneum acts protectively against these organisms is further suggested by the following facts. Simliar culture mediums to those which have been described, inoculated from material obtained from thirteen patients in whom the serosa over the tumor was cultured by swabbing with a sterile cotton swab immediately after opening the abdomen and exposing the tumor, remained sterile in most instances. Staphylococci, large gram-positive bacilli, diphtheroid organisms and indifferent streptococci, obviously of no significance, grew in a few instances.

With the knowledge that streptococci and colon bacilli are the chief offenders in and around malignant colonic lesions, and owing to the fact that the visceral peritoneum acts protectively, it would seem of vital importance to establish a specific or nonspecific relationship between intraperitoneal vaccination and the mechanism of its protection. At first thought, we would say there is specific local and possibly also general immunity against the two chief offending bacteria. This view must be maintained unless very positive and convincing proof is brought forth to the contrary.

The work of Morton [4] suggests that various substances can be used to immunize the patient intraperitoneally against lethal doses of hemo-

4. Morton, H. B.: Nonspecific Peritoneal Immunization, Proc. Staff Meet., Mayo Clin. **4**:209 (July) 1929.

lytic streptococci. He used bacterial filtrates, dextrose and a physiologic solution of sodium chloride and found stimulation of peritoneal defense with all. He also noted that the mechanism of such local immunity was by local peritoneal irritation, which called forth numerous macrophage cells, and phagocytosis of the hemolytic streptococci was carried on by these. However, the number of his animals was too small to allow of the conclusion that these nonspecific substances would serve as well as the vaccine produced from the organisms which seemed to be at least in part responsible for the etiology of peritonitis in human beings.

An outstanding detail of Morton's studies is the fact that some immunity can be produced in twenty-four or forty-eight hours, but much greater and more nearly complete immunity results from periodic injections over a period of six days. It would seem, then, that if enough rabbits were given injections of such substances as the streptococcus-colon bacillus vaccine, dead typhoid bacilli or milk and dextrose, if their omentums were sectioned and the peritoneal exudate studied for degree and extent of phagocytosis, and if animals were protected by these methods and then similar lethal doses of living streptococci and colon bacilli were injected into each and their peritoneal cavities and the degree of reaction studied, and if agglutinins could be demonstrated in the blood of these rabbits, the problem of what form of immunizing agent it would be best to use should be answered. Furthermore, after resection, a comparison of specimens of omentums or colonic mesenteries of patients who had had vaccine and those who had not, might give definite clews as to the nature of the mechanism of peritoneal immunity in the human being. A large series of freshly resected malignant lesions, from patients who had had vaccine and from those who had been operated on without vaccine, was studied for cellular infiltration in and about the tumor. Only the usual lymphocytic infiltration occurred. It was evident, therefore, that if any change was to be seen in the vaccinated and nonvaccinated patients, sections of omentum or mesentery distant from the malignant lesion should be studied. A collection of such specimens is being made, and a study of animals along similar lines is being carried out. All of the reagents produced leukocytosis in rabbits. The leukocytosis from the streptococcus-colon bacillus vaccine is by far the most marked. There was no gross evidence of peritoneal reaction in any of the rabbits which received whole autoclaved milk. In only one of those which received dead typhoid bacilli was there any gross evidence of peritoneal reaction. In 75 per cent of the rabbits which received the streptococcus-colon bacillus vaccine there was gross evidence of peritoneal irritation in the form of exudation of material grossly resembling fibrin.

Into five series of rabbits (four in each series) were injected intraperitoneally, after the methods described elsewhere, antiperitonitis vac-

cine, whole autoclaved milk, suspensions of killed typhoid bacilli like those used for fever therapy, hypertonic dextrose solution, and sodium chloride solution, respectively. The four animals were killed twelve, twenty-four, forty-eight and seventy-two hours, respectively, after injection and it was noted that the cellular infiltration both with polymorphonuclear leukocytes as well as macrophage cells of the omentums of the rabbits was greatest in those which had had the antiperitonitis vaccine mixture of streptococci and colon bacilli.

Other series of rabbits, all of the same size and general appearance, and all seemingly in good health, were given intraperitoneal injections of the same materials: vaccine of a mixture of streptococci and colon bacilli, killed typhoid bacilli, hypertonic dextrose solution, sodium chloride solution and whole autoclaved milk. The injections were made according to methods described by Hermann and found suitable as described elsewhere, and forty-eight hours after the last intraperitoneal injection large doses of equal suspensions of living green-producing streptococci and colon bacilli were given.

All the rabbits that had the injections of milk died, half of the rabbits that had typhoid bacilli and half that had sodium chloride solution died, all with fulminating generalized fibrinopurulent peritonitis. None of those that had been given antiperitonitis vaccine and none of those receiving dextrose died

These experiments are being continued by adding to the numbers of animals and varying the intervals between injections. The results will be reported in detail by Kellum.

The experimental, as well as the clinical, evidence is in favor of rather transient peritoneal immunity. However, the intraperitoneal route of the injection is of vast importance. As in animals, the most favorable time for resection seems to be forty-eight hours after the second intraperitoneal injection of the vaccine.

In several of the cases in which the patients died, vaccine was given in anticipation of resection, and then, because of local fixation or the situation of the lesion, only colostomy was performed. Subsequently, it was thought that perhaps the vaccine from the first procedure would suffice, and resection was undertaken without further vaccination. Others, treated similarly, had much severer postoperative courses than those who received vaccine in the routine way preoperatively, that is, two and five days before resection.

It has become necessary or has seemed wise, occasionally, to operate on the patient within twenty-four hours after the administration of the vaccine; the peritoneal injection and hyperemia in these instances have been noteworthy. On several occasions the surgeon has thought of the possibility of colitis because of the hyperemia of the serosa of the colon;

this suggests the value of drawing the blood supply to these parts and with it, of course, increased numbers of phagocytic types of cells.

The method of preparing the vaccine and its administration seem important. The organisms used for the vaccine are procured from the peritoneal exudate in a case of peritonitis. The vaccine prepared from the streptococci and colon bacilli so obtained is injected, in physiologic solution of sodium chloride, with a dulled spinal puncture needle, into the peritoneal cavity.

There are other important preoperative factors that make for a smoother convalescence and lower mortality rate in these cases of malignant disease of the colon. They include thorough cleansing of the large intestine, and particularly relief from obstruction. This has been accomplished in various ways, including the giving of a residue-free diet consisting primarily of fruit juices and candy; up to 3,000 calories are consumed in each period of twenty-four hours. Some laxative is given, and the colon is irrigated with physiologic solution of sodium chloride twice daily. At times this is best accomplished by giving such irrigations with the patient in the knee-chest position. Occasionally, hot abdominal stupes and withholding of food by mouth become necessary. Other measures of rehabilitation have included blood transfusions, control of carbohydrate metabolism and of urinary dysfunction, prevention of infection of the upper respiratory tract, and all other measures of seeming importance in preparation of a patient for an extensive surgical maneuver. Spinal anesthesia, also, holds a place of primary importance in any consideration of surgical procedures on the colon. Experimental, laboratory and clinical experience with these cases suggests that intraperitoneal vaccination is one of the most important steps in cooperative management of patients with malignant lesions of the colon.

The basis of this report is the 222 cases in which vaccine was given between Jan. 1 and Oct. 1, 1929, and fifty-eight cases in which operation was done in the course of these months, for similar conditions, and in which vaccine was not given.

A review of the eleven deaths from peritonitis, which occurred among the 222 patients operated on, suggests consideration of types of operations in cases included in this review. The patients operated on had all forms of surgical maneuver that are applied to the colon at the Mayo Clinic. Many of them, of course, underwent two or more major surgical procedures, as in all the graded resections. For this reason, the small number of eleven deaths from peritonitis is noteworthy. The tabulation shows the types of disease and the surgical procedures attempted in the eleven fatal cases.

Although these eleven cases include several in which the usual procedures in operating on the colon at the Mayo Clinic were employed,

cases necessitating unusual procedures are also listed. Some very extensive operations were required in greatly debilitated patients.

The fifty-eight patients with malignant lesions of the colon operated on during the same period, who did not receive vaccine, had lesions of similar situation and nature as those of the 222 who received vaccine. Of the fifty-eight patients, thirteen died of peritonitis; the operative procedures on the thirteen included four abdominoperineal resections, one Mikulicz operation (first stage), one ileostomy, one cecostomy, one colostomy, one ileocolostomy, three posterior resections of the rectum and one secondary resection of a lesion of the left part of the colon.

Summary of Eleven Cases of Peritonitis

Case	Age	Sex	Type and Situation of Lesion	Factors Relating to Risk	Anesthetic	Surgical Procedure
1*	67	M	Carcinoma of rectum	Age, peritoneum opened widely	Regional; amytal‡	Posterior resection after preliminary colostomy
2	60	..	Carcinoma of transverse colon	Obesity; complete obstruction; abdominal stupes necessary; omentum in ventral hernia; extensive operation	Spinal	Ileostomy and first stage of Mikulicz
3	70	M	Carcinoma of rectosigmoid	Fixed tumor with obstruction; much manipulation in determining possible operability	Spinal	Colostomy
4	74	M	Carcinoma graded 3 of rectosigmoid	Age; high grade of malignancy; extensive operation	Spinal	Colostomy and anterior resection
5	48	F	Carcinoma graded 3 of rectosigmoid	High grade of malignancy; lesion fixed and obstructive; obesity and hypertension	Spinal	Colostomy and anterior resection
6	44	M	Carcinoma of rectosigmoid	Fixation of lesion and soiling of field	Regional; amytal‡	Posterior resection after preliminary colostomy
7	48	M	Lymphosarcoma, 15 by 10 by 10 cm. of ascending colon	Local perforation of growth two days before operation	General	Resection of right half of colon for perforated lesion
8†	30	M	Carcinoma of transverse colon	Obesity; loss of 35 pounds in weight in short time; hemoglobin 36 per cent; intussusception of large lesion incorporating the stomach	Spinal	Colostomy
9	43	M	Carcinoma of rectum	....	Spinal	Colostomy and combined abdominoperineal resection
10	47	M	Carcinoma of rectosigmoid	.....	General	Anterior resection; lesion brought out as in Mikulicz; end-to-side anastomosis
11	44	..	Carcinoma graded 3 of transverse colon	High grade of malignancy; rapid loss of weight; small bowel attached to growth	Spinal	Resection for obstruction; forced resection of part of small bowel

* Contributing lethal factor, cellulitis.

† Contributing lethal factor, bronchopneumonia.

‡ Iso-amylethyl barbituric acid.

COMMENT

These studies emphasize the value of preoperative protection against peritonitis in procedures in which resection of parts of the large intestine are involved. That the intraperitoneal vaccination is one of the major parts of our preparation is demonstrated by the following facts: In the same week the same surgeon has operated on two patients of the same general build and age and otherwise offering a similar surgical risk, with lesions in identical situations, and has employed the same surgical maneuver, but one patient received vaccine and the other did not. The first patient died within five or six days, from generalized peritonitis; the second made a smooth, uneventful recovery. Except for the vaccine, the preoperative measures in both cases were the same.

It has been amply demonstrated that protection against lethal peritonitis can be established in animals. The relatively transient nature of such immunity is noteworthy. The time element between vaccination and operation is important. The amount of vaccine injected has less significance, but is important. The systemic reaction of the patient is often moderately severe, but endures only a short period, and is never alarming.

That the logical preventive reagent is a vaccine prepared from streptococci and colon bacilli is suggested by the predominant presence of these organisms in the exudate in fatal cases of peritonitis and their vast predominance in and around malignant lesions of the large intestine. Future experimental work and the method of trial and error should establish the best reagent for this mechanism of protection against peritonitis.

ILEOCECAL CYSTS *

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Cysts of the ileocecal region constitute a definite pathologic and surgical entity. That they are enterogenous developmental cysts, there can be no doubt. While the nature of these cysts is now well understood, the cause of their origin remains obscure. In many of the lower animals, the arrangement of the cecal pouches is suggestive. Ileocecal cysts are rare. A search of the literature yielded but twenty cases. It is evident, however, that many cases have been overlooked. With a growing appreciation of the condition, one may expect a marked increase in the number of cases reported.

Cysts and diverticula of the intestine apparently escaped the notice of the older pathologists.

In the small intestine, diverticula and cysts are found between the leaves of the mesentery, where the vessels pierce the wall of the intestine, leaving a point of lessened resistance.

In the large intestine the mucosal hernias or diverticula escape into the fatty appendices epiploicae, also a spot of lessened resistance. Owing to the fact that these diverticula are covered with fat, it is easy to understand their being overlooked. Roentgen examination often reveals them when their presence has not been suspected. About 5 per cent of all routine gastro-intestinal roentgen examinations show diverticula.

In pig embryos from 6 to 14 mm. long, diverticula of the duodenum are found regularly. In slightly older pig embryos diverticula are found throughout the small intestine and occasionally in the cecum.

Cysts and diverticula of the intestines are in reality different phases of the same process. They result from the growth of a bud or from a prolongation of epithelium which has pushed out into the mesenchyme. The mesenchyme, as far as the intestine is concerned, consists of all the other layers of the intestine except the epithelial or mucosal lining.

After the bud has pushed its way into the mesenchyme it becomes vacuolated. If an opening into the intestine is effected, a diverticulum results; on the other hand, if the bud becomes separate, a cyst is formed. The walls of these cysts always contain the elements of intestinal structure.

In this connection, it is unwise to speak of true and false cysts, as all are of similar origin, varying only in combinations of the different layers of the intestinal wall which enter into their formation.

* Submitted for publication, April 28, 1930.

It is possible that some cysts are formed in a different manner. To understand their origin better, one must for a moment revert to the embryologic development of the intestinal tube. In human embryos, Tandler found that a marked proliferation of the duodenal mucosa begins about the thirtieth day, resulting in complete occlusion of the intestine on the forty-fifth day. Then vacuoles begin to appear, and by the sixtieth day this lumen is again wide open.

The same process of epithelial proliferation and occlusion, with later canalization, occurs throughout the whole intestinal canal, but not with the great regularity seen in the duodenal segment.

Forssner maintained that congenital occlusions which persist are from mesoderm. Buds of mesoderm—young valvulae conniventes—push through the dense masses of epithelial cells which fill the lumen and meet similar buds from the opposite side. They coalesce, thus forming a bridge or septum. Carroway's case seems to show this clearly. In his case the lower end of the cecum, with the appendix opening into it, was completely shut off from the intestinal canal by such a septum.

Kreuter believes that such septums are formed from the epithelial elements, which become transformed into connective tissue.

The diagnosis of ileocecal cysts and cysts of the cecum is by no means easy. In most cases in which the diagnosis is made preoperatively, it can at best be only a shrewd guess. Even with the abdomen open, the exact nature of the condition cannot always be told. In some cases the final decision must await the microscope.

A movable tumor in the region of the cecum is suggestive. If the patient is a child the probability of ileocecal cyst is increased, although advanced age by no means excludes the condition.

A large percentage of the cases have shown symptoms of acute or recurring obstruction. In two of the cases reported in the literature, and in one of mine, intussusception existed concomitantly. Acute appendicitis has been the diagnosis in at least four of the cases reported. At operation the diagnosis can usually be made if a knowledge of this pathologic condition exists.

Both patient and surgeon will fare well if resection of the intestine is done. In no case has the attempt to enucleate the cyst been successful. I shall report three new cases.

REPORT OF CASES

CASE 1.—A child, aged 9 months, was admitted to the hospital with symptoms of acute intestinal obstruction.

Physical examination showed a tumor somewhat larger than a hen's egg in the region of the cecum. It could be moved slightly from side to side and was not tender.

Operation.—A right rectus incision revealed a tumor connected with the mesial wall of the cecum and the terminal ileum. The tumor was about 3 inches (7.6 cm.) long and 1 inch (2.5 cm.) by 1½ inches (3.77 cm.) in cross-section. There were two grayish-white spots on the wall of the tumor. As the lumen of the cecum was encroached on greatly, it was decided that resection should be performed. Accordingly, about 2 inches (5 cm.) of the terminal ileum, together with the cecum and appendix and 3 inches of the ascending colon, were removed, and side to side anastomosis was done.

The child recovered and was living and well two and a half years later. The child is now normal in all respects.

Pathologic Report (Dr. George S. Graham).—Gross Description: The specimen consisted of a segment of intestine 16.5 cm. long (fig. 1). It consisted of terminal ileum with the ileocecal valve near one end and beyond it about 4 cm. of cecum. Immediately above the junction of the small with the large intestine there was a protruding tumor mass 3 cm. in diameter with a smooth serous-

Fig. 1.—Intramural cyst of the ileum. The cyst produces an inward bulging of the wall of the bowel, beginning just above the fold of the ileocecal valve at the left. Its cavity has been opened by transverse incision. A probe projects from the appendical opening.

covered surface. It had been opened by transverse incision, which revealed it as a cyst lying within the wall of the bowel. On the serosal side the wall of the cyst was dense, almost cartilaginous, and was from 0.4 to 0.6 cm. thick. The muscular layer of the bowel could be followed into it. The inner wall or roof of the cavity was thinner but was also firm and appeared to contain smooth muscle. It was covered by the intestinal mucosa, beneath which the cyst bulged to form an elevation measuring 3.5 cm. in the longitudinal axis of the bowel and 1.5 cm. in the transverse axis. This elevation began just above the edge of the ileocecal valve. The cyst was lined by a smooth, dense, grayish-white tissue. In the mesenteric tissue were several lymph nodes, the largest being 1 cm. in length. They were natural in color and consistence.

Microscopic Description: The cyst cavity was lined by a thin mucous membrane. This was best seen in blocks taken from the outer wall or the floor of the cavity (serosal side of the bowel) (fig. 2). Where best developed, it showed

a surface layer of high columnar cells dipping downward into short, wide crypts. Opening into these singly, or in groups of two or three, were short, wide, tubular glands lined by polygonal cells with clear vacuolated cytoplasm, like that typical

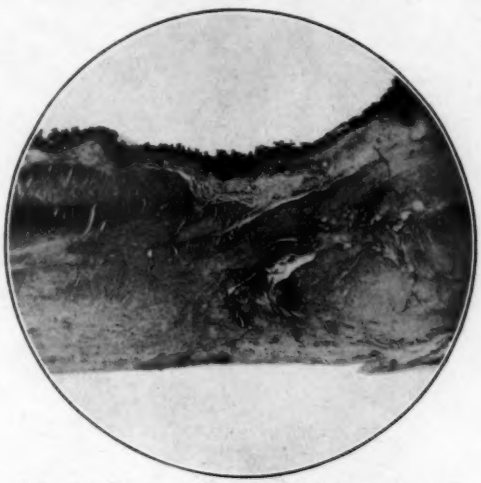

Fig. 2.—Outer wall or floor of the cyst; × 7.

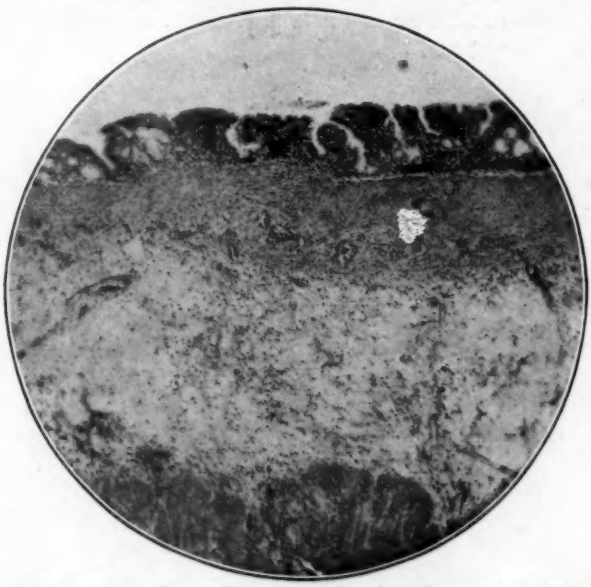

Fig. 3.—Outer wall or floor of the cyst, showing the mucosal lining; × 120.

of Brunner's glands (fig. 3). The larger surface depressions often extended more deeply and subdivided the tissue into irregular papillary formations or outlined thinner villus-like structures. The tunica propria was relatively dense. In some blocks this atypical mucosa flattened into a single layer of columnar

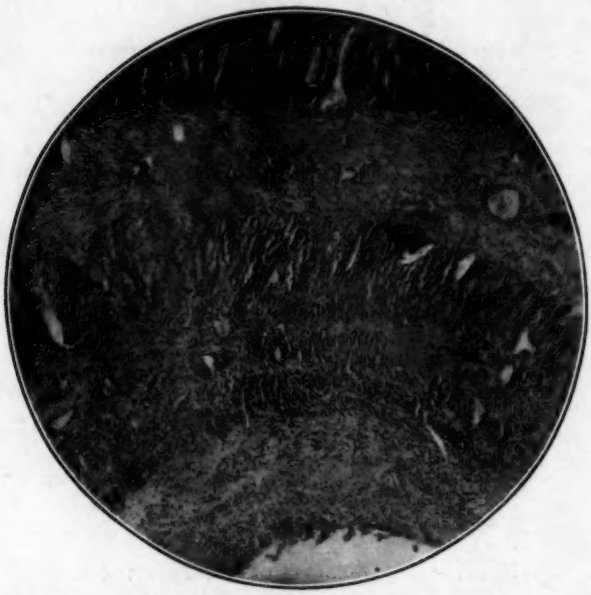

Fig. 4.—Inner wall or roof of the cyst. The lower level of the covering colonic mucosa can be seen at the top of the field. At the bottom is the denuded inner layer of the cyst cavity; × 120.

Fig. 5.—Angle of junction of wall of the bowel with the cyst. At the left is the uninvolved ileum; at the upper right, the cyst cavity; × 7.

epithelium with a thin supporting stroma and occasionally small sectors containing a few abortive glands. The flattening became more pronounced about the side walls of the cavity, and in the roof even this thinned mucosa disappeared, and the stroma was infiltrated by leukocytes. When present, the lining epithelium usually rested directly on a thick stratum of smooth muscle with irregularly disposed longitudinal and transverse strata, but this layer was absent in some sectors. Beneath it was a zone of connective tissue with infiltrating lymphocytes and eosinophils. Outside this there was a muscular wall of varying structure. In the floor it was thick and in general circularly disposed, but this thinned toward the roof where it was usually represented by two layers separated by a middle fibrous stratum (fig. 4). In the angle in which the normal wall of the bowel met the cyst, its longitudinal layer was continued in the floor of the cyst. The circular layer appeared to split, sending a thick layer into the floor and the thinner bundles upward into the roof (fig. 5). In both areas, the muscle bundles appeared to mingle with bundles proper to the wall of the cyst itself.

CASE 2.—A child, aged 2 years, was admitted to the hospital with a history of vomiting and bloody stools of six days' duration.

A mass could be felt by rectal examination, and a tumor was palpable in the sigmoid region.

Figure 6

Figure 7

Fig. 6.—Intramural cyst of the ileum. The outline of the ileocecal valve fold is seen just to the right of the cyst. A probe has been passed into the lumen of the appendix and projects beneath the valve.

Fig. 7.—Section through the cyst in the transverse axis of the bowel. The "roof" is collapsed from shrinkage while in the preserving fluids; × 2.

Operation.—At operation a large intussusception was found. It was impossible to reduce the intussusception, as the ileum had sloughed in two places. Resection of all of the colon with its contained intussusceptum, leaving only the sigmoid, was done. The ileum was joined to the sigmoid by lateral anastomosis.

The patient died one hour later.

The cecum showed a small cyst on its posterior wall just above its ileocecal valve.

Pathologic Report (Dr. George S. Graham).—Gross Description: The specimen consisted of a segment of bowel 8.5 cm. long (fig. 6). The vermiform appendix was attached near one end. On section the ileocecal valve was found near this end with the appendix opening beneath it. On the ileal surface of the valve there was a dome-shaped cyst 1.7 cm. in diameter and 0.8 cm. in height. The wall was thin, and the cavity contained a colorless fluid. The appendix emerged through the wall of the bowel just alongside and beneath the cyst.

Microscopic Description: Sections showed an epithelial-lined cyst apparently lying within the inner muscular layer of the small intestine. The outer wall or floor of the cyst (the side toward the peritoneum) was lined by a mucous membrane containing simple tubular glands opening through relatively large pits. They were lined by high columnar cells with vacuolated cytoplasm. There were large vacuolations suggesting that of the "goblet cell" but no tinctorial suggestion of contained mucus. The short rounded or slightly elongated end-pieces were lined by an epithelium of similar appearance. The cells suggested those of Brunner's glands rather than those of the small intestine. There were no cells of Paneth. The tissue was best developed at one lateral angle of the floor of the cyst (fig. 7) where it formed a thick layer with large and richly branching papillary folds. Outside this area it rapidly thinned into a single layer of columnar

Fig. 8.—Higher power view, showing the junction of the ileal wall with the cyst; × 7.

cells. The tunica propria of the thicker area also thinned and disappeared, the epithelium resting directly on the smooth muscle of the wall. There was a discontinuous inner layer of smooth muscle, sometimes suggesting a muscularis mucosae but appearing for the most part merely as an inner layer of the enveloping tissue. As the muscular wall of the bowel met the cysts, its longitudinal muscle layer was continued in the outer wall or floor of the cyst. The circular layer appeared to split, sending a widened layer into the floor and a series of bundles upward about the sides of the cyst to its covering surface or roof (fig. 8). The tissue of the latter was poorly preserved and its exact structure could not be clearly made out but it appeared to consist of a delicate fibrous tissue with an occasional trace of smooth muscle. It was covered in part by the intestinal mucosa but this had disappeared in large part and the inner or cyst surface was also denuded. Clinging to the inner wall of the cyst was a little serous or fibrinous coagulum with desquamated epithelial cells and a few leukocytes and red cells in its meshes.

CASE 3.—In June, 1928, a woman, aged 21, was admitted to the hospital complaining of pain over the cecal region. There were tenderness and rigidity over McBurney's point. A diagnosis of acute appendicitis was made.

Operation.—Operation was performed by Dr. C. N. Carroway, of Birmingham, who permits me to report this case. At operation, a cyst was found occupying the lower end of the cecum; the appendix opened into the cyst. The caput cecum

Fig. 9.—Cecal cyst. The appendix has been opened longitudinally. Its lumen opens into the cyst cavity, which also has been partially opened by incision through the roof.

Fig. 10.—Low power view of the cyst. The section passes tangentially through the orifice of the appendix; × 2.

was excised, and the defect in the intestine was repaired by suturing cut edges together.

The patient made an uneventful recovery.

Pathologic Report (Dr. George S. Graham).—Gross Description: The specimen consisted of the caput cecum (fig. 9). There was a conical enlargement of its wall with the appendix coming off from its apex on the serosal side and its base bulging into the lumen of the bowel and apparently constituting a cyst wall. No appendical opening was present. The appendix was 4 cm. long and was

slightly constricted at its cecal attachment. Incision through its distal portion showed a thickened dense wall and pus-filled lumen. A probe passed inward through the lumen entered the cavity of a cyst lying within the cecal wall and producing the deformity noted. It was filled with purulent fluid. It did not communicate with the lumen of the bowel. The muscular layer of the bowel appeared to cover the cyst on its serosal side, where it formed a thick dense wall. A thinner wall supported the colonic mucosa covering it on the side of the lumen of the bowel.

Microscopic Description: Sections through the cyst showed that it was located within the mucous layer of the colon (fig. 10). The muscular layers of the bowel lay in its outer wall or floor and were continued outward in the appendix

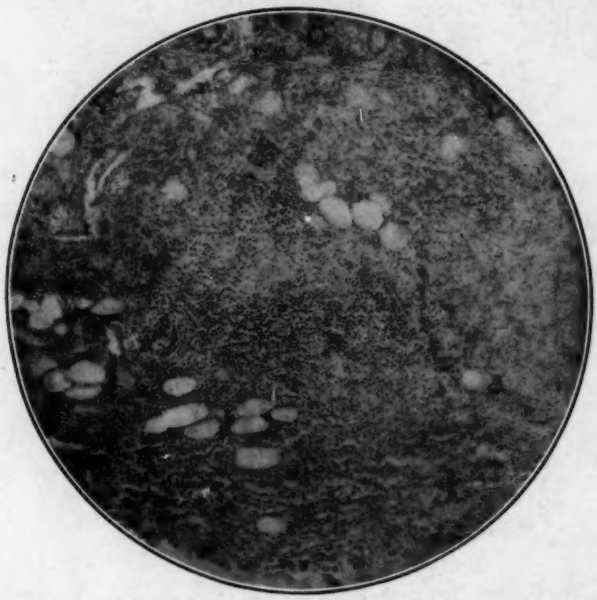

Fig. 11.—Roof of the cyst. The lower margin of the covering mucosa can be seen at the top; the cyst cavity is just within the field at the bottom. There is inflammatory exudate in the whole thickness of the wall; × 120.

where this structure communicated with the cyst cavity. The roof of the cavity consists of colonic mucosa supported on a layer of loose fibrous tissue containing occasional fat cells and continuous with the submucosa of the enveloping wall of the bowel (fig. 11). Immediately about the appendical orifice the inner surface of the cyst cavity was lined by typical colonic mucosa (fig. 12). Elsewhere no trace of mucosa was found, the inner loose fibrous tissue of the wall being infiltrated by great numbers of leukocytes and in places broken up by miliary abscesses (fig. 13). The leukocytes were mostly neutrophils, but there were occasional lymphocytes and plasma cells, endothelial leukocytes and in places many eosinophils. The inflammatory exudate spread laterally in the mucosa of the colon about the cyst and outward in the muscularis and serosa of the floor of the cyst. There was slighter extension outward in the proximal appendix, but the mucosa of the latter was well preserved.

Fig. 12.—Junction of the appendix with the cyst cavity. The section passes tangentially to the lumen at its upper end; × 7.

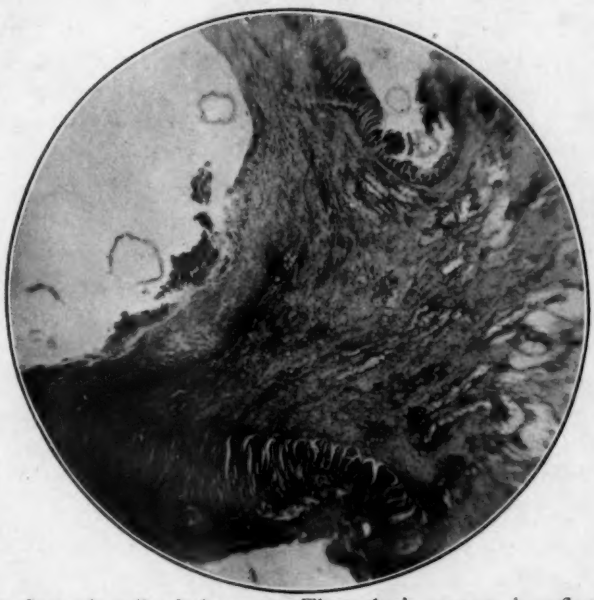

Fig. 13.—Lateral wall of the cyst. The colonic mucosa is reflected over its roof at the upper left; the muscular coat of the bowel passes to the left in the floor of the cyst; × 7.

REVIEW OF VERIFIED CASES IN THE LITERATURE

In 1882 Frankel [1] reported the first case of ileocecal cyst to be found in the literature. A child died three days after birth, with symptoms of intestinal obstruction. At autopsy a cyst 2½ inches (6.27 cm.) in diameter was found at the ileocecal junction. It projected into the ileum and the cecum. No microscopic examination was done, but the age of the child and the observations at autopsy are undoubted evidence that this was a genuine ileocecal cyst.

In 1886 Sainsbury [2] reported the case of a girl, aged 11, who had died of typhoid. At autopsy a large cyst was found in the cecum just above the ileocecal valve.

In 1896 Hueter [3] reported a cyst the size of a cherry stone situated at the ileocecal valve. It was covered only by mucosa.

The case Sprengel [4] recorded in 1900 occurred in a girl, aged 15 years. A laparotomy was done for suspected tuberculous peritonitis. The cecum was resected for tumor. A cyst 1¼ inches (3.14 cm.) long was near the ileocecal valve in the cecum. It was covered by serosa, and did not communicate with the lumen of the intestine. Microscopic examination showed columnar epithelium, tubular glands, lymphoid tissue and a few muscle fibers.

In 1902 Hedinger [5] described a case in a boy, aged 4. The cyst was very large and occupied a large part of the lower part of the abdomen. It contained a liter of milky fluid. It was attached to the mesentery of the ileum 10 cm. from the ileocecal valve. Section showed a peritoneal coat, two muscular coats, muscularis mucosae and an epithelial lining. The lining showed cylindric epithelium and flattened epithelium for the most part, and in some places epithelium was missing.

In 1903 Krogius [6] reported a case in a child, aged 2 months. The diagnosis was intestinal obstruction. At operation, a cystic tumor the size of a pigeon's egg was found in the ileum near the cecum; ileostomy was performed. A few days later excision of the intestines was done, but the child died of hemorrhage two hours after the operation. While no microscopic observations are given, Krogius reported it as an enterogenous cyst, which it probably was.

In 1906 Ayer [7] reported a case in a man, aged 23, who was operated on for a condition supposed to be appendicitis, accompanied with severe

1. Frankel: Virchows Arch. f. path. Anat. **87**:275, 1882.
2. Sainsbury: Tr. Path. Soc. **38**:146, 1886-1887.
3. Hueter: Beitr. z. path. Anat. u. z. allg. Path. **19**:391, 1896.
4. Sprengel: Verhandl. d. deutsch. Gesellsch. f. Chir. **29**:105 (pt. 1) and 537 (pt. II), 1900.
5. Hedinger: Virchows Arch. f. path. Anat. **168**:146, 1902.
6. Krogius: Ztschr. f. klin. Med. **49**:53, 1903.
7. Ayer: Am. J. M. Sc. **131**:89, 1906.

pain, vomiting and constipation. It was found, however, that the condition present was a thick-walled cyst, the size of a duck's egg. Here, as often occurs in these cases, even with the abdomen opened, the diagnosis was doubtful. The case was at first considered one of intussusception. However, the cecum was incised, and a cyst was found overhanging the ileocecal valve. No microscopic examination was made, but the thick-walled cyst was apparently lined with mucous membrane.

In 1910 Neupert [8] reported the case of a boy, aged 10, with a painful tumor in the ileocecal region.

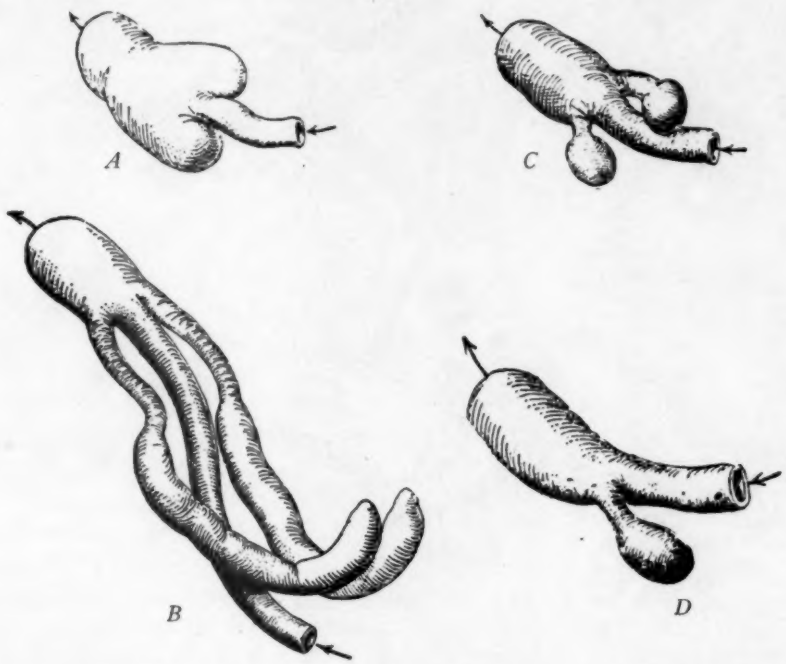

Fig. 14.—Types of ileocecal region (from Kelly: The Vermiform Appendix, 1905): *A*, two cecal pouches: American manatee, armadillo and many carnivorous birds. *B*, long cecal pouches of herbivorous birds (long narrow neck and small orifices): Goose, hen, owl, loon, ostrich, etc. *C*, short cecal pouches, narrow neck: little anteater. *D*, prolongated pouch and reduction in caliber in mole and spiny anteater.

At operation a tumor the size of a hen's egg was found in the terminal ileum, 4 inches (10.16 cm.) from the ileocecal valve. The cyst was enclosed on all sides by muscularis of the intestines and was lined by cubical epithelium with traces of mucosa.

8. Neupert: Centralbl. f. Chir. **37**:714, 1910.

In 1912 Baldwin [9] reported a case of true diverticulum of the cecum, with a history of appendicitis-like attacks which had occurred twelve and 7 years previously. A hard globular tumor 2 inches in diameter was found springing from the cecum at the ileocecal valve. It contained hard feces and communicated with the cecum by an opening which just admitted the tip of the finger. There was no pedicle, but a clamp was applied next to the cecum and the tumor cut away. On microscopic examination it was found that the wall of the tumor contained all the coats of the normal cecum. The patient recovered.

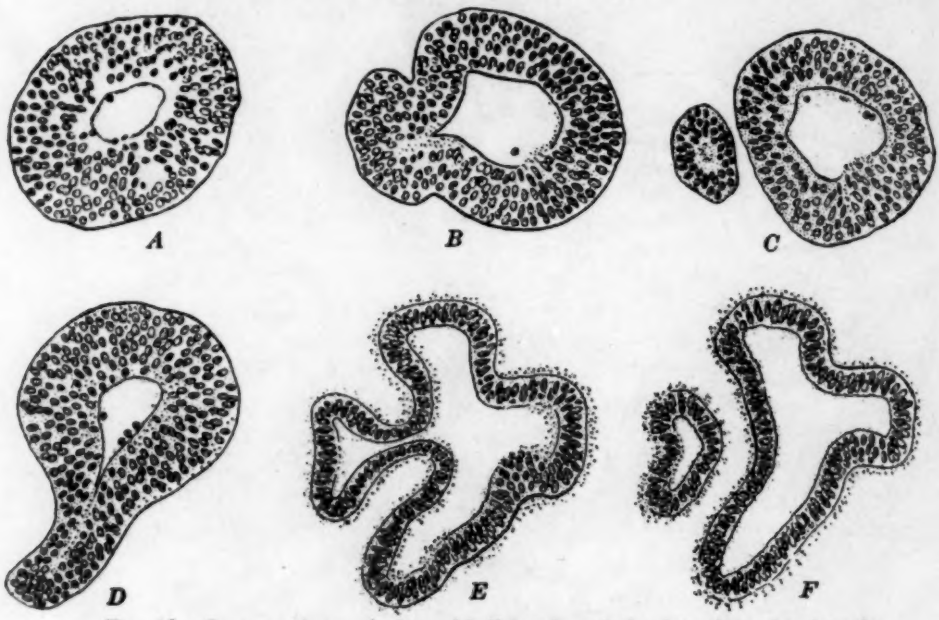

Fig. 15.—Cross-sections of the epithelial tube of the intestine, showing the development of diverticula; × 130. *A-D*, from an embryo of 22.8 mm. (Harvard Collection, Series 871). *E* and *F*, from an embryo of 30 mm. (Harvard Collection, Series 913). (After Kreibel and Mall: Human Embryology, 1912, vol. 2, p. 381.)

In 1913 Blackadder [10] reported a case which was described as a retention cyst of the cecum. It occurred in an infant, aged 10 weeks. The tumor projected into the cecal lumen. Section showed a cyst covered with mucous membrane similar to that of the intestine. It was lined with a thin layer of columnar epithelium, which was folded in places and showed gland formation. Beneath the epithelium was a distinct submucosa then three distinct layers of muscular fibers. It was undoubtedly an enterogenous cyst.

9. Baldwin: M. Rec. **81**:991, 1912.
10. Blackadder: Tr. Am. Pediat. Soc. **25**:296, 1913.

Turner and Tipping,[11] in 1914, described a case in a child, aged 4 months. At operation, a cyst 1 inch (2.5 cm.) in diameter was found encroaching on the lumen of both the ileum and the cecum. Its wall contained the coats of the normal intestine.

In 1914 Ball [12] reported a case in a child, aged 3 months. At operation the condition was thought to be an irreducible intussusception. Resection was carried out; when the colon was incised, a tensely distended cyst was seen to project from the wall of the cecum, blocking the ileocecal valve.

Bolton and Lawrence,[13] in 1916, reported a case in a child, aged 3 months. The cyst was in the mesentery at the ileocecal angle. It seemed to be incorporate with the wall of the cecum and the terminal ileum. It was incised, and glairy white, odorless fluid escaped. The greater part of the wall of the cyst was cut away. After prolonged drainage of similar fluid, the wound closed. Later, incision was required on two occasions to liberate a similar collection of fluid from the cavity.

In 1923 MacAuley [14] reported a case in a girl aged 6 months. After the intussusception was reduced a tumor could be palpated at the ileocecal valve. Resection was performed.

In 1925 Bazin [15] reported a case of intussusception in a boy aged 8 months. After the intussusception was reduced, a hard mass was found on the mesial wall of the cecum just above the ileocecal valve. The lumen of the cecum was encroached on. The cecum was resected. The child lived. Microscopic examination showed that the outer wall contained mucosa, submucosa and two muscular layers, all comparable to that of the adjoining cecum. It was lined by a thin layer of cuboidal cells.

In 1925 Lotheissen [16] reported a case in a woman aged 21. He found a large cyst in the interior of the cecum. He resected the ileocecal region, after failing to enucleate the cyst.

In 1928 Edwards [17] operated on a girl aged 12, who was thought to have acute appendicitis. A cyst 3½ inches (8.87 cm.) long and about 1½ inches (3.77 cm.) in diameter was in the right wall of the cecum, just above the ileocecal valve. It contained the structures of the wall of the intestine.

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11. Turner and Tipping: Proc. Roy. Soc. Med. **7**:29, 1913-1914.
12. Ball: Brit. J. Dis. Child. **2**:259, 1914.
13. Bolton, C., and Lawrence, T. W. P.: Brit. M. J. **2**:248, 1916.
14. MacAuley, H. F.: Brit. J. Surg. **11**:122, 1923.
15. Bazin, A. T.: Canad. M. A. J. **15**:130, 1925.
16. Lotheissen: Deutche Ztschr. f. Chir. **179**:394, 1923.
17. Edwards, Harold: Clin. J. **57**:319 (July 4) 1928.

In 1929 Evans [18] reported a case in a man, aged 29, who was operated on for a variable tumor in the cecal region. At times a distinct tumor could be felt, and again no sign of it could be found. It contained milky mucoid fluid. The walls of the cyst contained all the elements of the cecal wall, of which the cyst was really a part.

Resection was carried out with prompt recovery.

Evans also reported a case found in a specimen in the Royal College of Surgeons Museum (specimen no. 1221.1). It consisted of "a spherical retroperitoneal cyst 4 inches in diameter, intimately connected with the lower end of the ascending colon.

"Histologically the wall of the cyst consists of fibrous tissue with intermingled unstriped muscle fibres, lined with well developed mucus secreting epithelium. Here and there the surface raised into low papillae."

In 1929 Beekman [19] reported a case in a girl aged 5½ years. A diagnosis of partial intestinal obstruction was made, the possibility of intussusception being kept in mind. At operation, a cyst about 1½ inches in diameter was found encroaching on the ileum and cecum and connected with the mesial cecal wall. It contained a thick, glairy, yellowish, mucoid fluid. The edges of the cyst were sewn to the parietal peritoneum. A fecal fistula developed. This was closed by a second operation seven months later. The child has since remained well.

CONCLUSIONS

Cysts of the ileocecal region constitute a definite entity.

They are enterogenous developmental cysts. True diverticula of this region have the same origin.

Malignancy has not been noted in connection with these cysts.

Three of the twenty-three cases have been associated with ileocecal intussusception.

Resection of the terminal ileum and cecum is the surgical procedure of choice.

Dr. George S. Graham supplied the pictures for these case reports.

18. Evans, A.: Brit. J. Surg. **17**:34 (July) 1929.
19. Beekman: Ann. Surg. **90**:1097 (Dec.) 1929.

THE CLOSED METHOD OF TREATMENT OF FRACTURES OF THE ANKLE JOINT *

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My object in this paper is to report the methods and discuss the results obtained in the closed reduction of recent fractures of the ankle joint at the surgical clinic of the University of Milan.

The choice of methods to be employed in the treatment of these fractures is still a matter of discussion. Lambotte,[1] Lane,[2] Leclerc,[3] Alglave,[4] Berard, Picot,[5] Duval,[6] Basset [7] and Juvara advocated operative reduction in the fracture with marked displacement, for the following reasons: (1) A better reduction can be obtained, and the fragments are maintained in better apposition; (2) the time required for union is less, and (3) function is more quickly reestablished.

Guillembot, Tuffier, Delbet,[8] Lusena, Matti,[9] Lussana,[10] Leveuf, Girode, Monard and Monod prefer, as a rule, closed reduction. They expressed the belief, however, that operative reduction is not infrequently indicated, as, for instance, in those cases in which there is pluridirectional displacement of the foot; when there is a large anterior or

* Submitted for publication, March 14, 1930.

1. Lambotte, Abbin: Chirurgie opératoire des fractures, Paris, Masson & Cie, 1913.

2. Lane, W. A.: Les conséquences disastréuses de certaines fractures par abduction du cou-de-pied, Lancet **2**:697, 1921.

3. Leclerc, G.: Le traitement des fractures de Dupuytren par le vissage de la malléole interne, Bull. et mém. Soc. de chir. de Paris **48**:1267, 1922.

4. Alglave, P.: Au sujet de la technique du traitement sanglant des fractures bimalléolaires à grand déplacement, Bull. et mém. Soc. de chir. de Paris **50**:152, 1924.

5. Picot, G.: L'intervention sanglante dans les fractures malléolaires, J. de chir. **21**:529, 1923.

6. Duval, Pierre; and Basset: Indication et technique du traitement opératoire des fractures récentes fermées du cou-de-pied, Bull. et mém. Soc. de chir de Paris **49**:1415, 1923.

7. Basset, A.: Fracture récente du cou-de-pied: double fragment marginal postérieur: osthéosinthèse par vissage: excellent résultat anatomique et functionnel, Bull. et mém. Soc. de chir. de Paris, 1924, vol. 50.

8. Delbert, P.: Deux cas de fracture de Dupuytren, Bull. et mém. Soc. nat. de chir. de Paris **48**:421, 1922.

9. Matti: Die Knochenbrucke und ihre Behandlung, Berlin, Julius Springer, 1922.

10. Lussana: Le fratture del collo del piede, Arch. ital. di ortop. **42**:155, 1926.

posterior fragment of the tibia with a tendency for the foot to become dislocated again after it has been reduced; when the fractured malleolus and astragalus infringe on the remaining portion of the fractured internal malleolus, reduction thus being prevented, and, lastly, when the malleolar fragments become crossed and locked so that the foot remains in the abducted position.

Baldo Rossi,[11] Savariaud,[12] Soligoux,[13] Ferry and Delbet expressed the belief that reduction can be accomplished and maintained by the closed method in every type of fracture through the ankle joint, however complex. They also were of the opinion that the results obtained by the closed method equal or surpass those obtained by the operative method. I recently had the opportunity of examining patients who had been treated for fractures through the ankle joint at the Surgical Clinic of Milan, and found that in 435 cases of this character it had not been necessary to resort to an operation, even in the more serious and complex cases with pluridirectional displacement of fragments.

The external displacement of the foot is the most difficult to correct. The valgus position of the foot occurs when the astragalus is no longer held in position as a result of a fracture or diastasis of the malleoli. The external dislocation of the foot must be completely corrected; otherwise, there will be complex dynamic and static changes in the mechanism of the ankle joint which is under great strain, even under physiologic conditions. If, in addition to the valgus position, a backward dislocation of the foot occurs as a result of a fracture of the posterior margin of the articular surface of the tibia, difficulties in treatment are increased. A perfect anatomic reconstruction must be secured before a good functional result can be obtained. At times good reduction can be secured; at other times reduction is difficult, even under anesthesia and with the aid of the x-rays because of (1) the amount of displacement, (2) the peculiar shape of the fragments, and (3) the relation of the soft tissues to the fragments. Many surgeons, especially the French, are inclined to treat these fractures by the open method, not only to secure a reduction of the fragments, but also to maintain reduction by fixing by nail or screw the external malleolus to the tibia, or by fixing the posterior marginal fragment to the tibia (Lane, Lambotte and others).

There is no doubt that good results may be obtained by these procedures, but we think that as good, if not better, results, can be obtained

11. Rossi, Baldo: Lussazioni associate a frattura e fratture associate a lussazione, Comunicazione al XVII Congresso di Ortopedia, Venezia, 1926.

12. Savariaud: L'appareillage des fractures bimalléolaires récentes, en adduction forcée constitute la procédé de choix: il doit être préféré à la méthode sanglante, Presse méd. **32**:377, 1924.

13. Soligoux: À propos du fragment marginal postérieur dans la luxation du pied en arrière, Bull. et mém. Soc. de chir. de Paris **38**:1470, 1912.

in most cases without operation. I believe that I am correct in saying that the closed method is to be preferred in the treatment of these fractures. Infection with serious consequences is the chief danger of the open operation. Stiffness of the joint will result if infection occurs. Delayed bony union, as the result of the use of foreign material and the intolerance of the tissues to it, must be considered as a distinct disadvantage of the open reduction of these fractures.

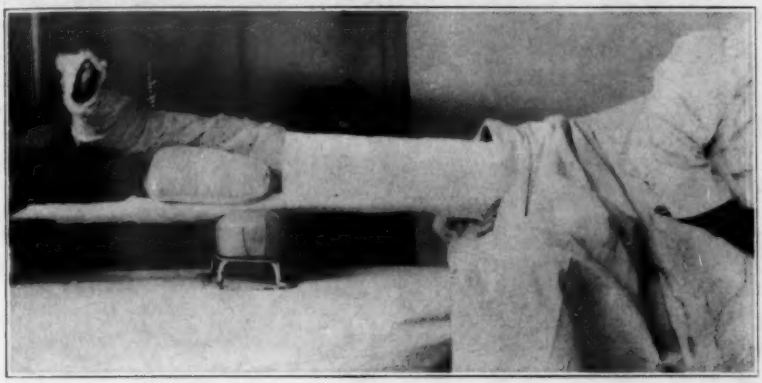

Fig. 1.—Construction of the temporary internal splint apparatus, showing arrangement of the cotton wool cushion between the splint and the lower third of the leg.

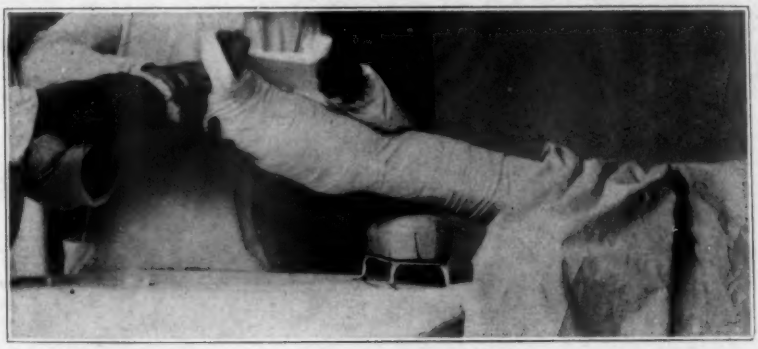

Fig. 2.—Showing the way to wrap the linen bandages in the construction of the internal splint apparatus in order to place the foot in the varus position.

When the closed method is employed, it is not good practice to apply a circular cast or to use even the Delbet dressing when the reduction is first made, because the reduction when first attempted may be difficult and incomplete, and again the dressing must be padded with absorbent cotton, because of the possibility of reactive and circulatory changes occurring about the fracture. Plaster loses a considerable part of its

fixation power when padded with absorbent cotton. Complete or partial recurrence of the displacement may occur as soon as the swelling is reduced and the dressing becomes loose.

When plaster is used there may be some difficulties in the reduction of fractures with marked and combined displacements, especially displacements lateralward and posteriorly. It is difficult to maintain

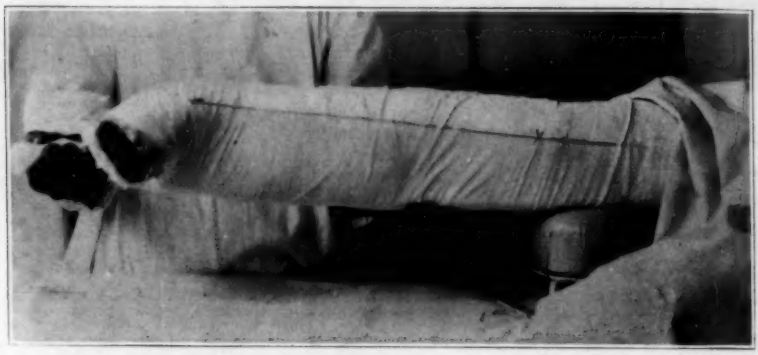

Fig. 3.—Degree of final varus of the foot obtained with the internal splint. It is is to be noted that the plantar surface of the foot is turned directly to the inner side.

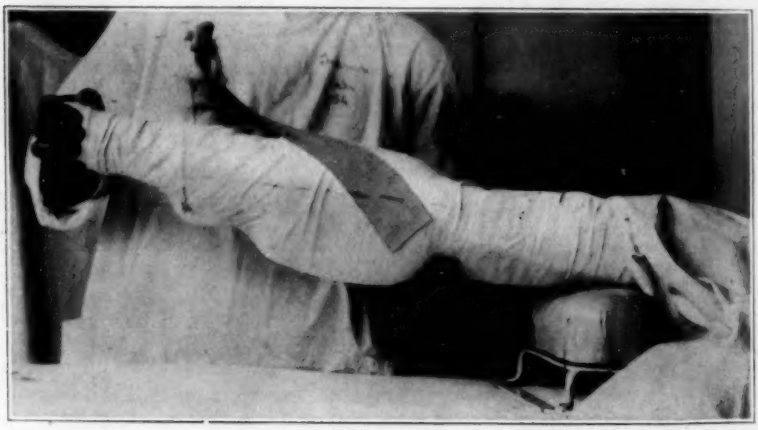

Fig. 4.—At the end of the construction of the internal splint apparatus the foot must be at right angle with the leg. This position may better be maintained by a traction plaster of paris stirrup.

reduction during the time required for the setting of the plaster. All the force used in the reduction will not be transferred to the foot by the plaster. For example, in the treatment of fractures of the neck of the femur, if the plaster used sets, a great part of the result of traction is lost when traction is released. In some fractures of the malleoli with

marked lateral displacement, in order to overcome the tibiofibular diastasis, to secure a good reduction of the fragments and to prevent a recurrence of the valgus position, it is necessary that the reduction be maintained by a force as powerful as that used in the reduction.

This is accomplished by a lever, to be described later, by which the fracture is reduced and reduction maintained. Even if all the force required could be secured by a circular plaster cast to maintain the foot in an overcorrected position, this would be undesirable because of the pressure that might develop with the subsequent edema and the consequent possibilities of gangrene. Sometimes one must be satisfied

Fig. 5.—Roentgenogram of a typical Dupuytren's fracture with marked tibiofibular diastasis in G. P., aged 49; valgus position and subtotal posterior luxation of the astragalus.

with incomplete reductions imperfectly maintained by padded dressings which do not maintain in good position the more marked displacements which tend to recur. In such cases, one may at times be almost ready to admit that open reduction has certain advantages.

The temporary lever apparatus used by Professor Baldo Rossi in the Surgical Clinic of Milan for the reduction of the lateral and posterior displacements of the foot is the Dupuytren apparatus, to which has been added some important modifications which make it more efficient. After the temporary reduction by this apparatus, plaster is used for immobilization.

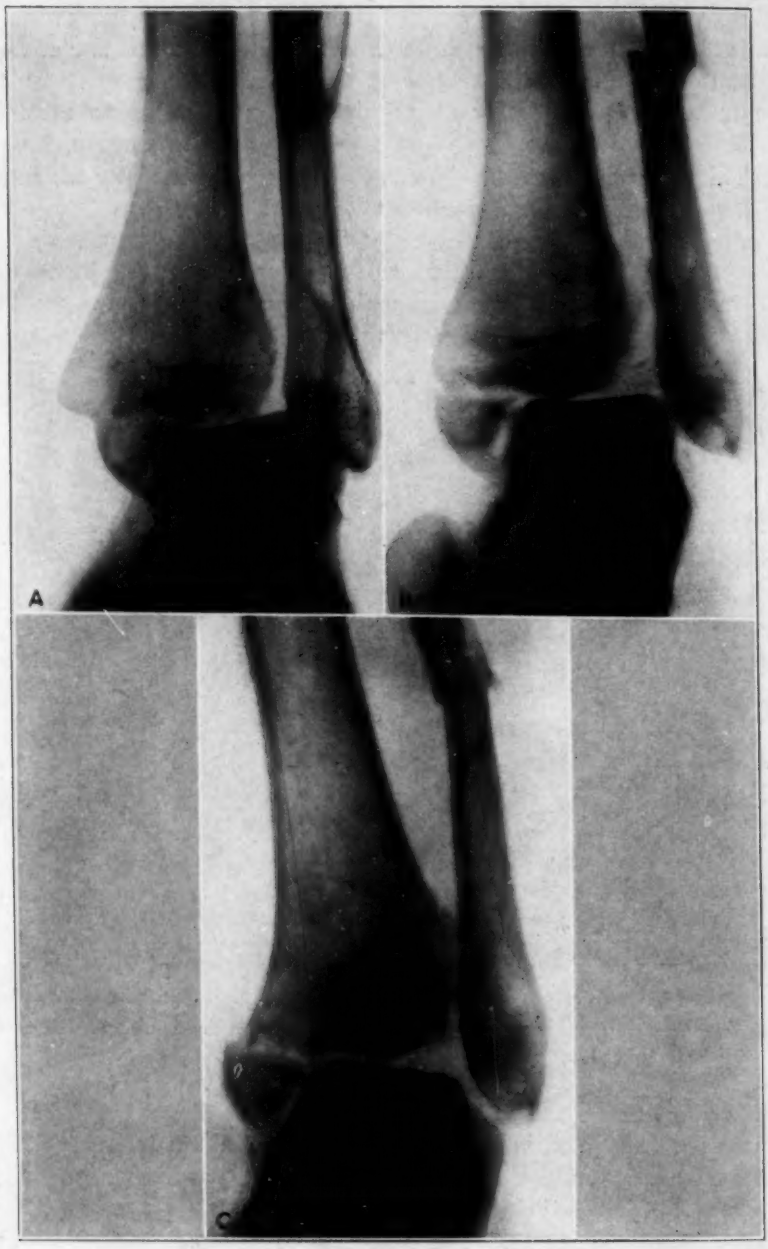

Fig. 6.—Roentgenograms of the same patient as in figure 5. *A* shows the first step of the reduction with the internal splint apparatus. The reduction is not complete. *B* shows the second step of the reduction with the internal splint apparatus. Although improved, the reduction is still incomplete. In *C*, the reduction of all the displacements (of the diastasis, of the internal malleolus and of the astragalus) is completed at the third applications of the internal splint apparatus.

A description of this apparatus and the way that it is used follows:

1. The lower extremity is covered with a layer of absorbent cotton. A wooden splint (from 90 to 100 cm. long, 6 cm. wide and 1 cm. thick) also covered with absorbent cotton is placed on the inner side of the extremity. It extends from the distal two thirds of the thigh distalward to 10 cm. beyond the plantar surface of the foot.

2. A large pad of cotton is now placed between the inner surface of the lower two thirds of the leg and the splint. The thickness of this pad must be proportionate to the degree of the varus position which it is desired to obtain.

3. The upper part of the splint is fixed by means of bandages which below include the cotton pad. There must be considerable space between the foot and the splint. This is secured by the cotton pad.

4. After manual correction of the gross displacement, the foot is forced, by means of bandages, tighter and tighter against and over the inferior third of the splint, so that the foot is in a marked varus position. In this way, the lateral displacement is corrected.

It is not always easy to secure the varus position at once. The reduction is secured by degrees by tightening of the bandages and corrective maneuvers about the heel. It would not be wise—frequently it is impossible—to secure by a single violent manipulation a complete reduction of the fragments in some of these cases. Occasionally the fracture cannot be reduced. This happens with other procedures, especially in attempts at manual reduction, reduction not being maintained when the plaster is applied. The operator may tire and therefore attempts to reduce the fracture more quickly, employing sudden and violent manipulations, which are interrupted. Muscular contractures, especially when the patient is not asleep (hence the frequent necessity of administering an anesthetic in this procedure), interfere greatly with the reduction.

The method advocated in this paper permits of gradual and progressive reduction. The muscle spasm is overcome gradually, and the traumatized tissues gradually accommodate themselves. The pain which the patient suffers is limited in intensity. Except in rare cases, an anesthetic is not required.

The bandage should be applied so that the roll when tightened causes a gradual reduction of the fracture with the foot in an overcorrected position. The bandage should be applied from without inward so that the foot is brought into the proper position as indicated in figure 2. Several rolls of the bandage should be tightly applied so that the reduction secured may be maintained. The foot must be kept at right angles or almost at right angles, for this position is most favorable for the reestablishment of function, especially so when there is a possibility of some stiffness of the ankle joint after immobilization.

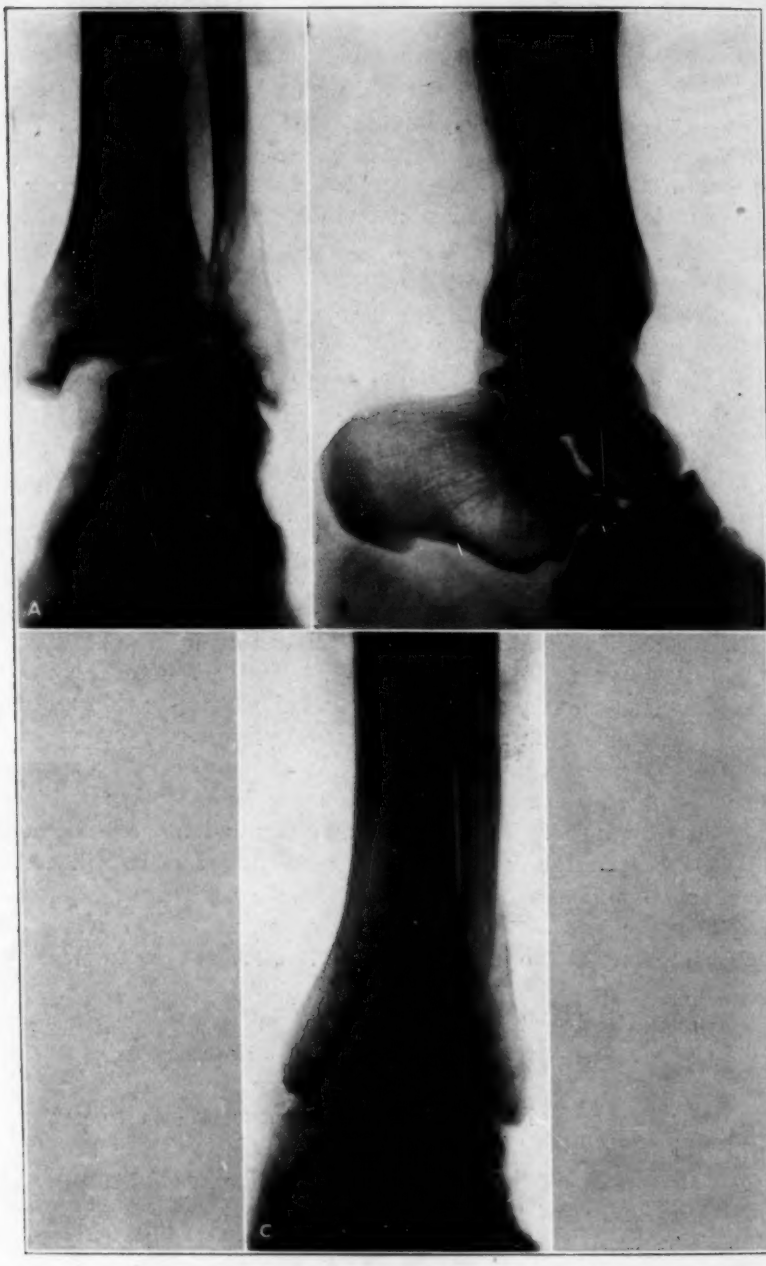

Fig. 7.—Roentgenograms (*A* and *B*) of a low Dupuytran fracture (instead of the fracture of the internal malleolus there is a tear of the internal lateral ligament), a posterior marginal fracture, valgus position, diastasis of the tibiofibular joint and external subluxation of the astragalus, in M. G., aged 51. *C* shows complete correction of every displacement with internal splint apparatus.

5. If in addition to the eversion, there is also a posterior dislocation of the foot, this must be corrected before the foot is brought into the varus position by bandaging it to the internal splint. Cases in which the dislocation is combined with a large posterior marginal fragment of the lower end of the tibia must be differentiated from those in which the posterior dislocation is the result of a marked diastasis of the tibia and fibula. In the cases of the first group pressure of the foot directed from behind forward must be maintained while the foot is brought pro-

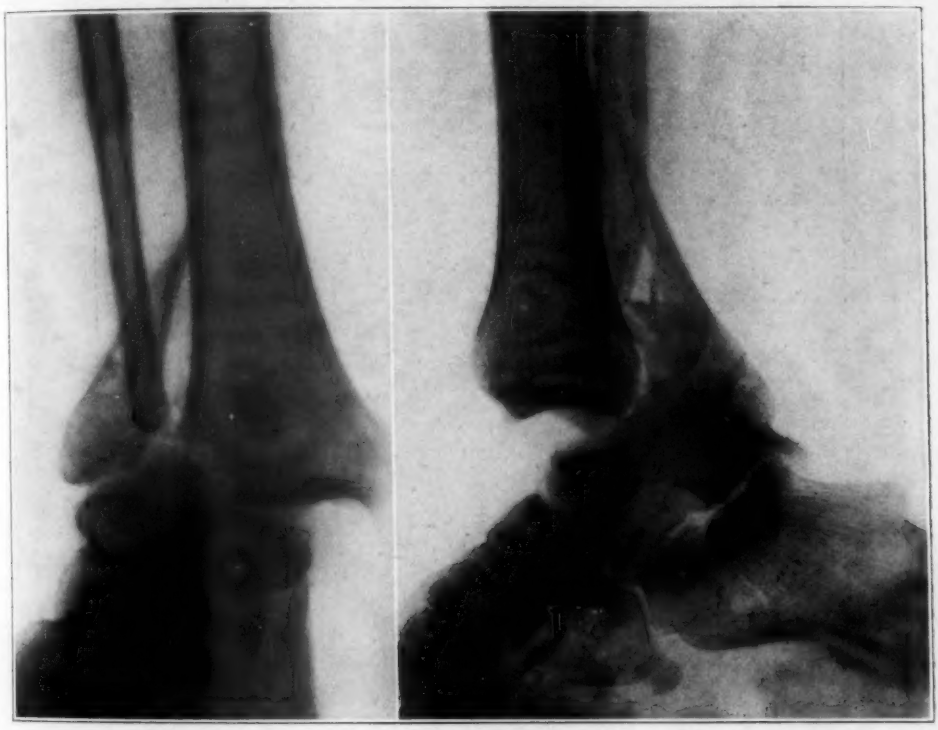

Fig. 8.—Roentgenograms showing a low Dupuytren's fracture and posterior marginal fracture of the tibia with diastasis, valgus position and posterior dislocation of the foot, in G. G., aged 37.

gressively into the overcorrected varus position, the foot being kept at a right angle. Such a procedure prevents recurrence of the posterior dislocation and also reduces the posterior marginal fragment. The dorsal capsular ligament of the tibia tarsal articulation is made tense, and the fragment is brought downward and forward until it is contacted with the fractured surface of the tibia. In the second group of cases in which the dislocation is dependent on the wide diastasis of the tibia and fibula, reduction is made more easily if before the foot is brought

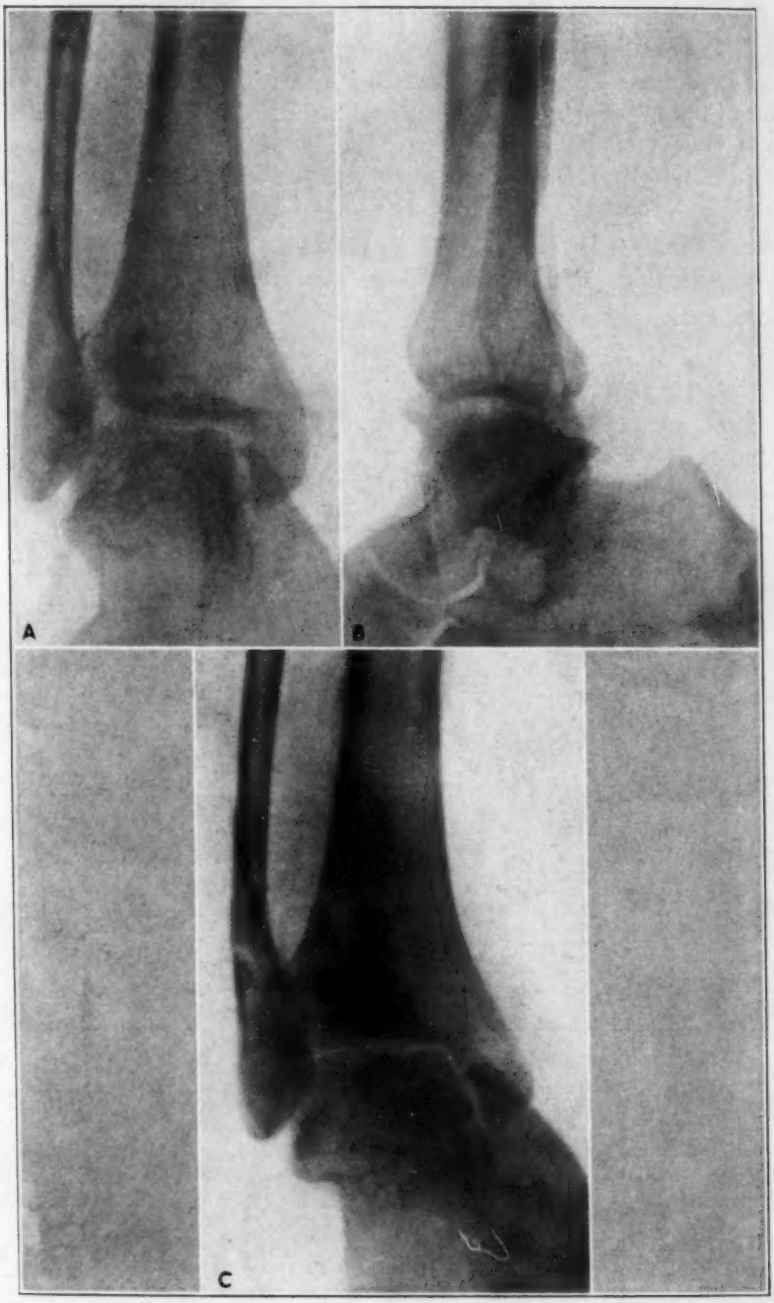

Fig. 9.—Roentgenograms of the same patient shown in figure 8. In *A* and *B*, with the first temporary internal splint apparatus, the posterior luxation of the foot has been reduced, while a light degree of tibiofibular diastasis still persists. In *C*, at a second application of the internal splint apparatus, the complete reduction of every displacement is obtained.

forward the valgus position is temporarily exaggerated so that the astragalus passes more easily over the posterior border of the articular surface of the tibia. When reduction occurs, there is a characteristic jerk. Reduction may be maintained without any special precaution while the bandage is applied about the foot and splint.

6. When reduction is completed, a roentgenogram must be taken at once in two planes in order to determine whether or not the results are satisfactory. If the correction is not satisfactory, the astragalus, although in supination, not bearing the proper relations to the articular

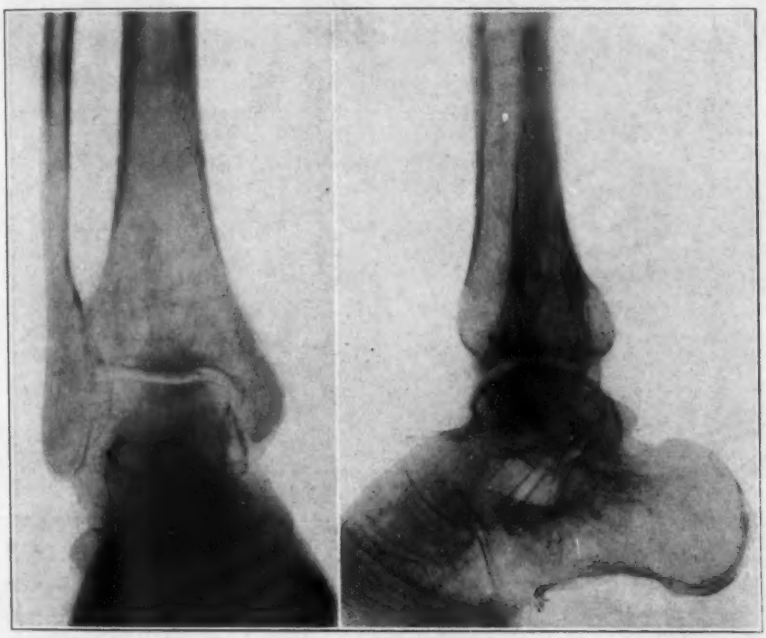

Fig. 10.—Roentgenograms showing good anatomic and functional result in G. G., after seven months.

surface of the tibia, or the lower fibular fragment not being placed in its proper relation to the tibia, attempts can be made deliberately to improve the results, preferably on the following day. The cotton pad used is replaced by a larger one, and the bandage is again applied as already indicated. There is no great hurry, for one of the advantages of this dressing is that the reduction may be made by degrees without traumatism of the tissues, for the muscular resistance is gradually overcome.

7. The temporary internal splint is left in position from eight to twenty days, depending on whether there is swelling of the soft tissues, the amount and complexity of the displacement and the time required in the different stages of reduction.

As a rule, if good reduction has been secured there is no necessity of changing the apparatus. If there is marked swelling of the tissues or abrasions and wounds of the skin which require attention, it will be well to reapply the dressing, which may become loose as the edema subsides.

The application of this dressing is not difficult or complicated. No special equipment is required. Reduction can be secured even when there is not complete muscular relaxation at first and when there are those bony displacements which many regard as making the fracture irreducible. The reduction is made by a powerful lever of the second

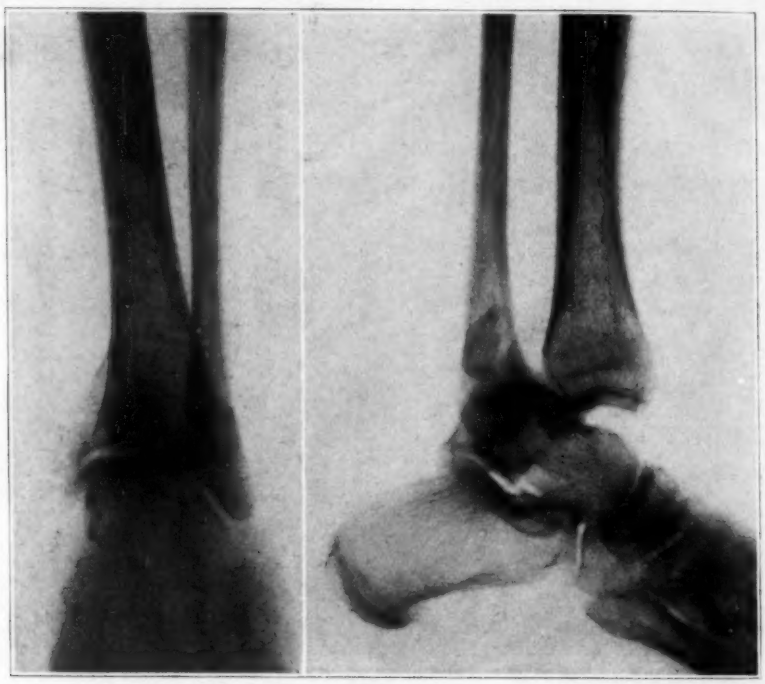

Fig. 11.—Roentgenograms showing internal malleolar fracture by adduction with a large fragment and posterior marginal fracture tibia with slight varus position and complete posterior dislocation of the astragalus and of the foot, in C. T., aged 19.

class, the fulcrum of which is formed by the cotton pad and force of which is produced by the tight bandage over the foot. The resistance is represented by the distal part of the splint. This is a lever with a continuous, progressive, graduated force.

When it is thought that a satisfactory reduction has been secured, this original dressing is removed and a circular plaster cast applied in order to maintain the reduction effectively. The plaster cast is applied over a stockinet fashioned to fit the leg and foot, so that the plaster will

be accurately adapted to the parts. A strip of cotton may be used over each malleolus to prevent pressure and over the upper and lower ends of the cast so that cutting of the skin will be prevented. If the cast is so applied, the displacements will not recur. The redisplacement of the posterior marginal fragment has been noted most frequently. The recurrence of this displacement has been regarded by some surgeons as a justification and indication for the open operation.

I believe that these recurrent displacements are due to the too early use of plaster before the edema has subsided and to employment of

12. Roentgenograms of C. T., showing complete and perfect reduction of every displacement in the temporary internal splint apparatus.

absorbent cotton beneath the plaster cast, especially if it is circular, which does not permit of firm fixation about the malleolar and dorsal surface of the foot, particularly if the tissues are swollen and edematous when the cast is applied.

The temporary internal splint maintains reduction even when the edema decreases, for it is more than a fixation apparatus; it acts as a lever which continues to act even after the displacement has been reduced. Although the cotton padding and the disappearance of the edema may lessen the power primarily exerted, this lever exerts enough

force which continues to act as long as the splint is left in position to maintain reduction.

The plaster cast extends as high as the tuberosities of the tibia as a rule, motion at the knee being permitted. In cases of more marked and serious displacements, the cast embraces the lower third of the thigh. If there has been a marked displacement of the fragments, it is advisable to take a roentgenogram even after the plaster has been applied to determine whether the reduction is satisfactory.

Fig. 13.—Roentgenograms showing subtotal separation of the lower epiphysis of the tibia with separation of a posterior cuneiform metaphyseal fragment and with supermalleolar fracture of the fibula; posterior and external deviation of the axis of the leg, in D. B. C., aged 15.

I prefer the circular cast to Hergott's so-called plaster gutter, the plaster splints of Maissonneuve and the apparatus suggested by Reclus and Delbet. A plaster cast applied from eight to ten days after a fracture carries no dangers and maintains reduction. Almost immediate, even if partial, use of the fractural limb is permitted. No further observation is required, and the patient can be dismissed the day after it is applied.

The cast is left on for thirty, sixty or seventy days, depending on the type of fracture. The cast must not be removed too early, and the formation of callus in malleolar fractures is frequently delayed. In order to secure good bony union, immobilization must be continued for more than two months. After such long immobilization the stiffness of the joint which may develop is of no marked significance, for it usually disappears in one or two weeks when physiotherapy or rational treatment is instituted.

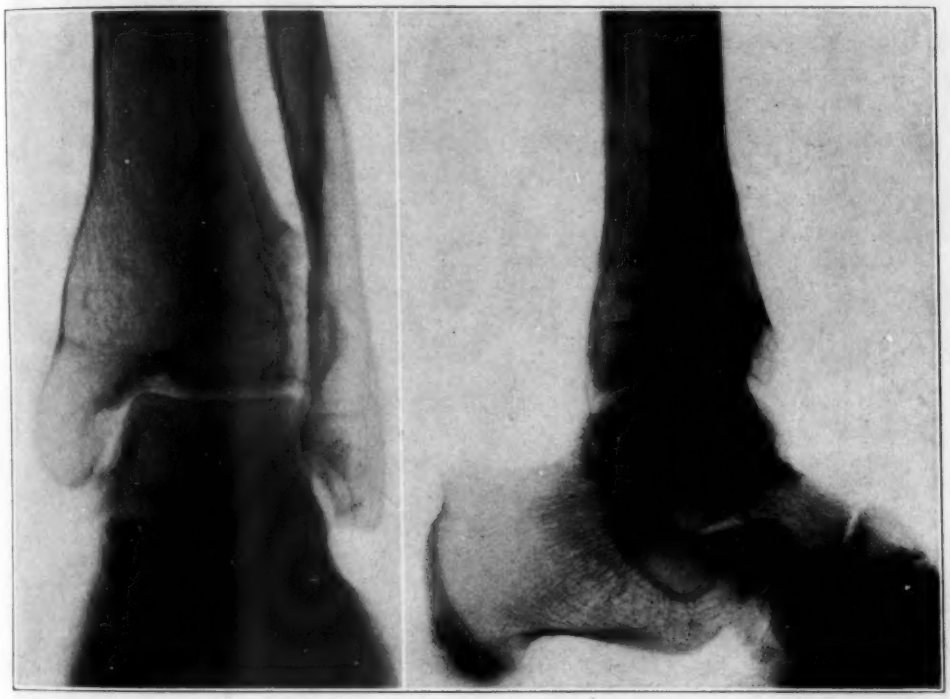

Fig. 14.—Roentgenograms of D. B. C. taken after four years, showing good anatomic and very good functional result.

When the cast is removed, an examination is made to determine whether or not there is good union. A roentgenogram should be made to determine the amount of callus formation. One can then judge whether or not it is best to permit of weight-bearing on the fractured leg. If movements of the foot and weight-bearing cause pain, and if the roentgenogram reveals fibrous callus insufficiently consolidated, a lighter cast is applied after gentle massage and passive motion of the foot has been instituted. This second cast may be worn twenty, thirty or forty days, depending on the case.

When the cast is finally removed, the after-treatment is begun; massage, hot baths, diathermy and artificial sun baths are employed to promote the circulation, reduce the edema and hasten the formation of bony callus and union.

Some of the results of this method of treatment are indicated in the figures appearing in the body of the article.

This method of overcoming the valgus position by use of the internal splint can also be used in supramalleolar fractures, and in epiphysial separations with or without a fracture of the metaphysis of the tibia when in the valgus position.

In conclusion, I believe that the closed treatment of fractures of the ankle joint, if properly employed, satisfies all the surgical indications. This statement applies to the more serious malleolar fractures with the marginal fragment of the lower end of the tibia and to those with pluridirectional displacements of the astragalus and of the foot. I believe this the method of choice in the treatment of these fractures, but do not deny that cases may be met in which an operation must be performed because the fragments cannot be reduced in any other way. In 435 consecutive fractures of this type observed by me no operation has been required.

THE REGENERATION OF HYALINE CARTILAGE IN JOINTS

AN EXPERIMENTAL STUDY *

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Before the work of Redfern [1] in 1851, it was thought that hyaline cartilage possessed little or no power of regeneration. Since that time the experimental studies on hyaline cartilage have shown that it possesses this property, but the investigators cannot agree as to the exact method by which it is brought about. The object of this communication is to review the more significant papers in the literature on the regeneration of hyaline cartilage in joints, ribs and ears, and to present the results of experiments on the injury and healing of hyaline cartilage in the joints of dogs. The literature of this country contains no experimental reports of such work in joints. Most of the reports have come from England, Germany, France and Italy.

Hunter [2] published an article, "The Structure and Disease of Articulating Cartilage," in which he said, "From Hippocrates to the present age it is universally allowed that ulcerated cartilage is a troublesome thing and that when once destroyed it is not repaired." It was in this article that the circulus articuli vasculosus, or the vascular border of the joint, was first described. Leidy,[3] following a series of experiments on cartilage, concluded that after the rupture of articular cartilage the fragments never unite. Kolliker [4] wrote that cartilage possessed no power of regeneration, nor did wounds of cartilage heal by a proliferation of the cartilage substance. In the same year, Paget [5] stated that there were no instances in which a lost portion of cartilage had been

* Submitted for publication, Feb. 7, 1930.

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1. Redfern, Peter: On the Healing of Wounds in Articular Cartilage, Month. J. M. Sc. **13**:201, 1851.

2. Hunter, William: On the Structure and Diseases of Articulating Cartilage, Philosophical Tr. Roy. Soc., London **9**:267, 1743.

3. Leidy, Joseph: On the Intimate Structure and History of the Articular Cartilage, Am. J. M. Sc. **17**:277 (April) 1849.

4. Kolliker, A.: Manual of Human Histology, London, Sydenham Society, 1853, vol. 1, p. 59.

5. Paget, James: Healing of Cartilage, Lectures on Surgical Pathology, London, Longman (and others), 1853, vol. 1, p. 263.

restored or a wounded portion repaired with new and well formed cartilage, and that the gap of cartilage in a fracture into a joint became filled with tough fibrous tissue.

Since 1850, a great many investigators have contributed a wealth of material to the subject of the regeneration of hyaline cartilage in joints. The best piece of experimental work in the early period was that of Redfern.[1] He showed that wounds in articular cartilages healed perfectly by the formation of fibrous tissue at the site of the injury. This fibrous cicatrix, he found, consisted of white and of yellow fibers, which were formed from the intracellular substances of the cartilage and from the nuclei of its cells, respectively. He observed that the cartilage cells lying near the cut surface might be enlarged and rounded or oblong in shape, that they were filled with corpuscles, and that occasionally they projected into the mass on the cut surface. These cells were in a position to discharge their contents whenever the cell wall should offer too little resistance to the escape of the contents. The stimulus of the incision was thought to have produced an abnormal development of the cells of the part through which it had passed. Redfern [6] demonstrated that after injury a fibrocellular layer was formed from the increased proliferation of cartilage cells, with an accompanying softening and fibrillation of the hyaline substance. This layer was firm enough to be torn off with its nipple-like processes from the cartilage, and not infrequently formed a permanent fibrous cicatrix.

Gurlt [7] concluded that the loss of cartilage substance could be repaired through fibrous tissue, which was sometimes like cartilage, but never fully cartilaginous tissue. The fibrous tissue was found to change itself by degrees into connective tissue cartilage and fibrocartilage. Gussenbauer [8] made the statement that wounds of the cartilage in which the bone was not broken did not heal.

Ogston [9] wrote of the focus of central growth in cartilage. He believed that the cartilage grew toward the joint surface, as well as toward the joint, from this central focus. This was in order to replace the loss of cartilage from the forces acting on the surface and to replace the cartilage surface toward the joint, which was being constantly

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6. Redfern, Peter: Observations on the Development and Nutrition of Bone and Cartilage and on the Relations of the Connective Tissues to Each Other in Health and Disease, J. Anat. & Physiol. **32**:96, 1897-1908.

7. Gurlt, E. F.: Beitrage zur vergleichenden pathologischen Anatomie der Gelenkkrankheiten, Berlin, 1853.

8. Gussenbauer, Carl: Ueber die Heilung per primam Intentionem, Arch. f. klin. Chir., 1871, vol. 12.

9. Ogston, Alexander: On Articular Cartilage, J. Anat. & Physiol. **10**:49, 1875-1876.

worn away. Ogston [10] further stated that articular cartilage was as valuable and necessary in forming and maintaining the structure and shape of bone as was the periosteum. The cartilage, however, unlike the periosteum could not in a short space of time proliferate laterally, but grew only toward the epiphysis, and if a portion was removed in making a perforation, the adjacent portions could not proliferate toward or into the perforation.

Tizzoni [11] reported that in cartilage covered with perichondrium the restoration of the cartilaginous tissue began in the perichondrium. In further experiments with joint cartilage, he found that on the edge of the incision the cartilage cells had become smaller and showed granular degeneration, while in the adjoining layers of cartilage the cells showed enlargement. He also observed fibrin formation in the matrix between the superficial and the adjoining layers of cartilage, which later was changed into cartilaginous tissue. He found that in incisions through the cartilage to the subchondral bone, there was a metaplasia of the fibroblasts of the marrow into new cartilage cells.

Prudden [12] described the changes that took place in the proliferation of the cartilage cells. There was found to be an increase in the bulk of the fibers of the intranuclear network and occasionally a definite grouping of these fibers into more or less conical-rayed figures at the opposite poles of the nuclei. The newly formed nuclei were sometimes enclosed in the body of the cell, but in many cases were seen lying completely outside of the latter and pressed closely against the capsule. In many cases, there was a distinct new formation of separate cells within the enlarged cavity; in others, there seemed to be simply a multiplication of the nuclei but no differentiation into separate cell bodies. When completely developed cells were formed, they were in no case separated by the formation of a partition of basement substance across the cavity, such as is seen in the proliferation of cartilage cells under normal conditions. He further observed that the absorption of the cartilage took place by cells growing in from the surrounding granulation tissue.

Gies,[13] in studying the healing of joint wounds in cartilage, showed that an aseptic wound of cartilage did not heal, but that an infected wound with maceration healed completely. He also observed that after trauma, there was an extensive degeneration of hyaline cartilage.

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10. Ogston, Alexander: On the Growth and Maintenance of the Articular Ends of Bones, J. Anat. & Physiol. **12**:503, 1878.

11. Tizzoni, Giudo: Arch. per le sc. med. **2**:28, 1878.

12. Prudden, T. M.: Experimental Studies on the Transplantation of Cartilage, Am. J. M. Sc. **82**:360, 1881.

13. Gies, T.: Histological and Experimental Study of Joint Disease: IV. The Healing of Wounds in Cartilage, Deutsche Ztschr. f. Chir. **18**:8, 1882.

Seggel [14] observed that after four days the young capsule forms of cartilage cells adjacent to the defect sometimes became decidedly enlarged and later formed mitoses. He demonstrated that after twelve days islands of loose cartilage in a defect started to become changed into connective tissue and took part in the formation of the scar. It was shown that cartilage reacted to trauma with proliferation of cartilage cells showing mitoses and formation of new hyaline matrix. These areas were always well circumscribed. Seggel further found that in an intact linear incision of cartilage after five months there was no reaction and that a superficial and central defect of cartilage remained more or less the same in this time.

Fasoli [15] found that after forty-six days there was protrusion of proliferated cartilage from the cartilage incision, and that after twenty weeks there was a complete repair of cartilage which had been cut through to the bone. Rimann [16] described a metaplastic cartilage formation in the deep defects in cartilage with no change along the edges of the cartilage. He showed that after thirty-one days the defect became filled with cellular connective tissue from the marrow, which was changed into cartilage. Ciociola [17] demonstrated that wounds of cartilage extending to the underlying bone presented a definite transition from connective tissue to hyaline cartilage, and that the tangentially placed superficial wounds which did not reach the bone showed scarcely any reaction after two months.

Fisher [18] contradicted Ogston's idea of a focus of central growth and stated that the superficial cartilage cells had the same function as the perichondrial cells of the lateral part of the articular cartilage, and were the parent cells of the more fully developed cartilage cells in the deeper parts. He also demonstrated that the repair near the margins of the articulating cartilage was good, but that nearer the center it was poor unless the underlying cancellous bone had been exposed. Fisher further showed that after six weeks the pared off cartilage from the condyle of the femur showed no sign of repair on the pared surface, but that the cartilage in the lateral part did show proliferation.

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14. Seggel, Rudolf: Experimentelle Beitrage zur Anatomie und Pathologie des Gelenkknorpels: II. Studien über Knorpelwunden und Defekte, Deutsche Ztschr. f. Chir. **75**:453, 1904.

15. Fasoli, G.: Sul comportamento delle cartilagini nelle ferite, Arch. per le sc. med. **29**:365, 1905.

16. Rimann, Hans: Experimenteller Beitrag zur Lehre von der Entstehung der echten, freien Gelenkknorper, Virchows Arch. f. path. Anat. **180**:446, 1905.

17. Ciociola, F.: Contributo allo studio della riparazione delle ferite delle cartilagini articolari, Policlinico (sez. chir.) **28**:229 (June) 1921.

18. Fisher, A. G. T.: A Contribution to the Pathology and Etiology of Osteoarthritis, with Observations upon the Principles Underlying Its Surgical Treatment, Brit. J. Surg. **10**:52, 1922-1923.

Ito,[19] experimenting with rats, proved that the defect in articular cartilage was first filled with granulation tissue which became fibrous and then was changed into fibrocartilaginous tissue, and finally into cartilage. In some of his experiments, it was demonstrated that the reparative tissue came from the underlying cancellous tissue, while in others transitional cartilage-like tissue seemed to arise in connection with the edges of the synovial membrane. Fibrous tissue was demonstrated filling the defect in one week, a transitional tissue between fibrous tissue and cartilage in two weeks, and islets of new cartilage in fibrous tissue in three weeks.

Haebler,[20] experimenting with the articular cartilage of dogs, found that when the cartilage alone was injured without injury to the subchondral bone, the cartilage wound showed no change after 300 days. This proved to him that the cartilage itself possessed no power of regeneration. When the subchondral bone was injured, as well as the cartilage, the cartilage defect became filled with fibrous tissue.

A great many of the experimental studies on the regeneration of hyaline cartilage have been with cartilage completely enveloped with a perichondrium, such as that found in the ribs and ears. Marchand [21] after experiments with costal cartilage concluded that cartilage wounds were healed by the proliferation of a layer of connective tissue from the perichondrium, which became partly changed into fibrocartilage. He found that the defect was first filled with fibrin. In about two weeks, the cartilage itself showed little change, but there was a thickening of the perichondrium. After four weeks there was a moderate fibrous thickening and a new formation of the hyaline cartilage tissue, which came from the perichondrium.

Matsuoka [22] and Mori,[23] both experimenting with cartilage of the ear in rabbits, confirmed the conclusion of Marchand. Malatesta,[24] experimenting with the costal cartilage of rabbits, stated that only exceptionally can the cartilage and connective tissue surrounding the

19. Ito, L. K.: The Nutrition of Articular Cartilage and Its Method of Repair, Brit. J. Surg. **12**:31, 1924-1925.

20. Haebler, C.: Experimental Study of the Regeneration of Joint Cartilage, Beitr. z. klin. Chir. **134**:602, 1925.

21. Marchand, F.: Healing of Cartilage Wounds, Der Process der Wundheilung mit Einschluss der Transplantation, Deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1901, pt. 16, chap. 18.

22. Matsuoka, M.: The Regeneration of Cartilage, Virchows Arch. f. path. Anat. **175**:1 (Jan.) 1904.

23. Mori, M.: Studies on Cartilage Regeneration, Deutsche Ztschr. f. Chir. **76**:220, 1905.

24. Malatesta, R.: Concerning the Healing of Aseptic Wounds of Hyaline Cartilage from the Perichondrium Covering the Normal Cartilage, Virchows Arch. f. path. Anat. **184**:123, 1906.

cartilage wound produce young connective tissue, which later may be changed into hyaline cartilage. This change of connective tissue always took place under the influence of the perichondrium.

Haas,[25] using the costal cartilage of rabbits for experiments, found that the regeneration of cartilage took place almost entirely from the perichondrium. It proceeded by direct proliferation of all the layers of the perichondrium beneath the outer fibrous tissue. There was found to be a slight amount of regeneration of cartilage from the original cartilage near the perichondrium, but the remainder of the cut end tended to undergo degenerative changes. He also observed that the proliferation of cartilage increased in amounts proportional to the length of time that had elapsed.

METHOD OF STUDY

Fourteen dogs were used in these experiments. In eleven the knee joint was used, in two the elbow, and in one the wrist. The dogs were first fully anesthetized with ether. The knee joints were opened under aseptic precautions, either by a curved infrapatellar incision with the patella tendon cut transversely, or by a long anterior incision with the quadriceps tendon cut transversely. The elbows were exposed by a posterior incision over the olecranon, the triceps tendon being incised transversely. The wrist was exposed by a transverse dorsal incision. The defects in the cartilage were made either with a 5 mm. burr through to the subchondral bone or with a scalpel. In some cases, only the most superficial layers of the cartilage were pared off with the scalpel; in others, the cartilage was removed down to the calcified matrix. The condylar ridges of the femur in most cases were traumatized by pounding with a small metal hammer for one minute. In all cases, the joints were closed with great care and all incised tendons carefully approximated. A light plaster cast was applied to the extremity after the operation and left on for from one to two weeks. The dogs were killed in one, two, four, eight and twelve weeks. After death, the blood vessels in the extremities were washed with saline solution, and then india ink was injected into them.

In the knee joint, defects were made in the following areas: patella, internal and external condyles of the femur, internal and external condyles of the tibia, internal and external condylar ridges of the femur, and the upper and lower intercondylar spaces of the femur. In the elbow, the defects were made with the scalpel in the head of the radius, the olecranon fossa of the ulna, the posterior lower humerus and the external and internal condyles of the humerus. In the wrist, defects were made with the scalpel in the scaphoid bone, the semilunar bone and the lower end of the radius.

Gross and microscopic examinations were made of the defects in the joints after the dogs had been killed. Unfortunately, some of the microscopic sections were not clearly cut through the defects, and cannot be included in the analysis of the observations. Sixty-six of the seventy-four sections were satisfactory.

25. Haas, S. L.: Regeneration of Cartilage and Bone with a Special Study of These Processes as They Occur at the Chondrocostal Junction, Surg. Gynec. Obst. **19**:604, 1914.

The observations have been grouped and analyzed in four ways:

1. According to the type of cartilage defect: (*a*) through the superficial layers, (*b*) through to the calcified matrix, (*c*) through to the subchondral bone and (*d*) due to trauma by direct force.

2. According to the time elapsed before the dogs were killed: (*a*) twelve weeks, (*b*) eight weeks, (*c*) four weeks, (*d*) two weeks and (*e*) one week.

3. According to the location of the defect in: (*a*) the patella, (*b*) the condyles of the femur, (*c*) the condylar ridges of the femur, (*d*) the intercondylar spaces of the femur and (*e*) the condyles of the tibia.

4. According to the presence or absence of the perichondrium.

REGENERATION IN CARTILAGE DEFECTS OF VARIOUS TYPES

Cartilage Defect Through the Superficial Layers.—Eight joints were used in this study, divided as follows: five knees, two elbows and one wrist. A sharp scalpel was used to pare off the superficial layers of cartilage. Three dogs were killed in eight weeks, two in four weeks, one in two weeks and two in one week.

Gross examination revealed no evidence of healing in the one and two week specimens. The greatest amount of healing in the four week specimens was in the external condyle of the tibia. Here there was noted a definite infiltration of the defect with fibrous tissue. The evidence of repair in the eight week specimens was more marked than in the four week ones. All of the defects in the cartilage were clearly ascertained and the presence or absence of attempted repair was noted.

The microscopic sections were satisfactory in twenty-seven of the twenty-nine areas studied. Five of the seven eight week sections showed regeneration. The clearest evidence of the regeneration of hyaline cartilage was noted in the head of the radius in one of the eight week sections; there were many large, deeply stained new cartilage cells, irregularly placed along one border of the cartilage, between which could be seen fibrils and in this fibrillar structure some blood vessels. Another eight week section of the head of the radius showed many young cartilage cells in the superficial layers about one corner of the defect. An eight week section of the lower intercondylar portion of the humerus presented some deeply stained branching cartilage cells, intermingled with loose connective tissue, which were regarded as evidence of regeneration. In eight week sections of the lower end of the radius and the semilunar bone, it was possible to see new, multinucleated, deeply stained cartilage cells. Three of the eight four week sections showed large quadrilateral cartilage cells on the surface of the defects. It was thought that these might represent an attempt at the formation of new cartilage cells. One two week section of the external condyle of the tibia (fig. 1), showed the defect filled with fibrin and granulation tissue, in which were some areas of new fibrocartilage. This defect was adjacent to the margin of the hyaline cartilage, and it appeared that the new fibrocartilage had originated from the old fibrocartilage that is normally present in this region. The cell columns of the deep hyaline cartilage layers on the side of the new fibrocartilage had turned their lines of axis toward the defect. This was thought to represent an early process of regeneration. There was a marked proliferation of perichondrium over the defect in one four week section of an internal condylar ridge, and this was also present in less degree in a four week section of the internal condyle of the femur. A defect in a four week section of the internal condyle of the tibia was partially filled with fibrous tissue, which contained some cartilage cells (fig. 2). One two week specimen of the external condyle of the femur, showed the defect filled with fibrin and pus cells, which had the appearance of undergoing

an organization into granulation tissue. One four week specimen of the internal condyle of the tibia and one two week specimen of the condylar ridges showed clefts in the cartilage, the former filled with fibrous tissue, and the latter filled with fibrin. Fibrin could be seen filling the defects in two eight week specimens, three two week specimens, and one one week specimen. Almost all of the sections showed a depression and irregularity of the cartilage edge, which took a pale stain and presented evidence of fibrillation and disintegration of the matrix.

Cartilage Defect Through to the Calcified Matrix.—There were eleven joints used in this study, divided as follows: seven knees, two elbows and one wrist. A sharp scalpel was used to pare off the cartilage down to the hard calcified matrix.

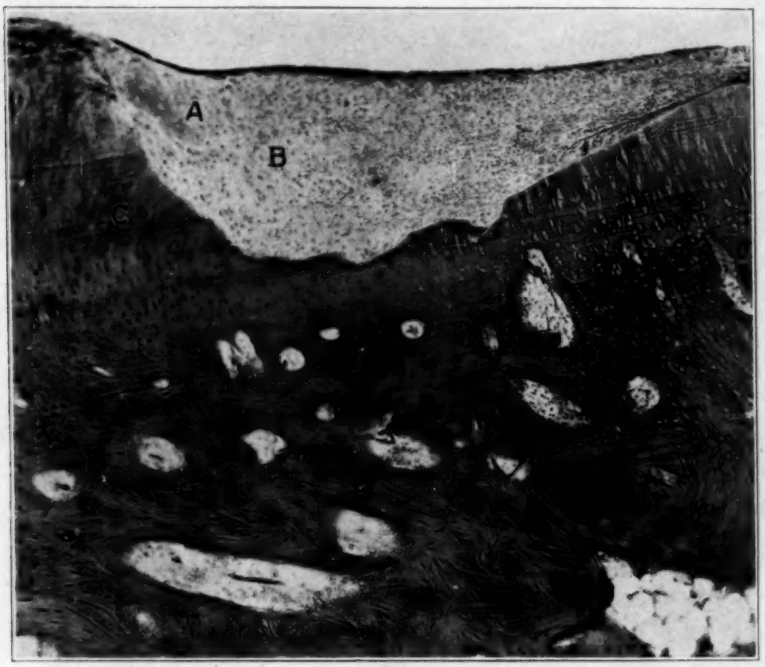

Fig. 1.—Regeneration of cartilage after two weeks in a defect extending through the superficial layers of the external condyle of the tibia (section 12 f under low power): *A*, area of new fibrocartilage; *B*, granulation tissue and connective tissue filling the defect; *C*, cartilage cell columns of deep layers bending toward the defect.

Two dogs were killed in twelve weeks, three in eight weeks, three in four weeks, one in two weeks and two in one week.

On gross examination, there was no evidence of healing in less than four weeks. The best evidence of healing was observed in the internal condyle of the tibia and the lower intercondylar space of the femur. The patellar surface in both of the twelve week specimens showed a definite smoothing off of the denuded area. The other denuded areas which showed healing were covered with a definite fibrous tissue growth. The scaphoid bone of the wrist in the eight week specimen presented excellent evidence of healing.

The microscopic sections were satisfactory in fifteen of the sixteen areas studied. All of the twelve week sections, one eight week section, and one four week section showed definite evidence of the regeneration of cartilage with the presence of new, deeply stained, large, multinuclear cartilage cells. No regeneration of hyaline cartilage was noted in less than four weeks. The new cartilage cells were found in a proliferation of connective tissue along the denuded margin of the patella in three sections, two of twelve weeks and one of four weeks (figs. 3 and 4). There were new cartilage cells adjacent to an increase in hyaline

Fig. 2.—Regeneration of cartilage after four weeks in a defect through the superficial layers of the internal condyle of the tibia (section 10 e, under high power): *A*, connective tissue pannus on surface of the defect containing spindle cells; *B*, nipple-like process of connective tissue extending into cartilage, containing oval cells and new cartilage cells; *C*, line of calcified matrix.

matrix along one condylar ridge, two patella margins and one scaphoid margin. This new hyaline matrix was lighter stained than the old matrix, and in some places had a fibrillar appearance. It apparently had been produced by the new cells. All of the fibrous pannus covering the denuded cartilage was well vascularized. A great many pale-staining, disintegrating islands of cartilage were observed along the outer edge of the proliferating tissue. There were also some islands of bone along this edge. This bony structure did not take as uniform a stain as the normal bone. Most of the exposed edges of the cartilage showed a

fibrillation of the matrix with an extremely light stain. Some of the denuded areas of the patella and olecranon fossa of the ulna presented areas of fibrocartilage adjacent to which was a proliferation of fibrous tissue containing cartilage cells. Deeply stained fibrin partially filled the defects in two of the one week sections.

Cartilage Defect Through to the Subchondral Bone.—Six knee joints were used in this study. The defects were made through the superficial and calcified cartilage layers with a small perforating burr about 5 mm. in diameter. Three dogs were killed in twelve weeks, two in four weeks and one in two weeks.

On gross examination, all of the defects in the twelve week specimens could be clearly recognized and showed evidence of healing. The two defects in the external condyle of the tibia showed the largest amount of healing. In none of

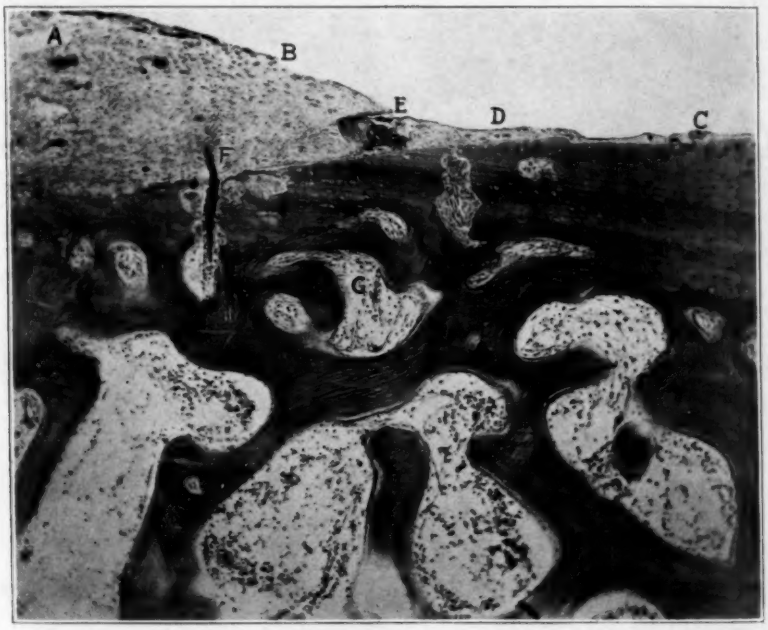

Fig. 3.—Regeneration of cartilage after four weeks in a defect through to the calcified matrix in the patella (section 7 a, under low power): *A*, pale-staining, disintegrating island of cartilage surrounded by connective tissue; *B*, new cartilage cells on edge of connective tissue pannus; *C*, new cartilage cells surrounded by new hyaline matrix along edge of calcified matrix; *D*, area shown in figure 4 with high power; *E*, bone nodule embedded in connective tissue pannus; *F*, blood vessel growing from subchondral marrow into connective tissue pannus; *G*, subchondral marrow surrounded by normal bone.

these, however, was there the normal glistening appearance of the adjacent nontraumatized cartilage. Fibrous tissue could be seen filling these defects. Granulation tissue filled the defect of one four week specimen. One twelve week experiment showed a defect in the external condyle of the tibia to be well filled with fibrous tissue, while a defect in the internal condyle of the tibia showed fibrous tissue in much smaller amounts.

Twelve of the seventeen microscopic sections studied were satisfactory. As was to be expected from the macroscopic appearances, the twelve week sections presented the greatest amount of regeneration. Three of these sections showed deeply stained, multinucleated cartilage cells (fig. 5). Fibrocartilage adjacent to areas of connective tissue containing cartilage cells was observed in contact with these areas of new cartilage cells (fig. 6). The defects were all well filled with connective tissue, which became more compact as the edge of the defect was approached. There were many detached islands of cartilage and bone in and on the surface of the defects. These apparently had been broken off by the burr in creating the defects. These islands of cartilage were poorly stained, showed disintegration, and in places were contiguous to fibrous tissue and cartilage cells,

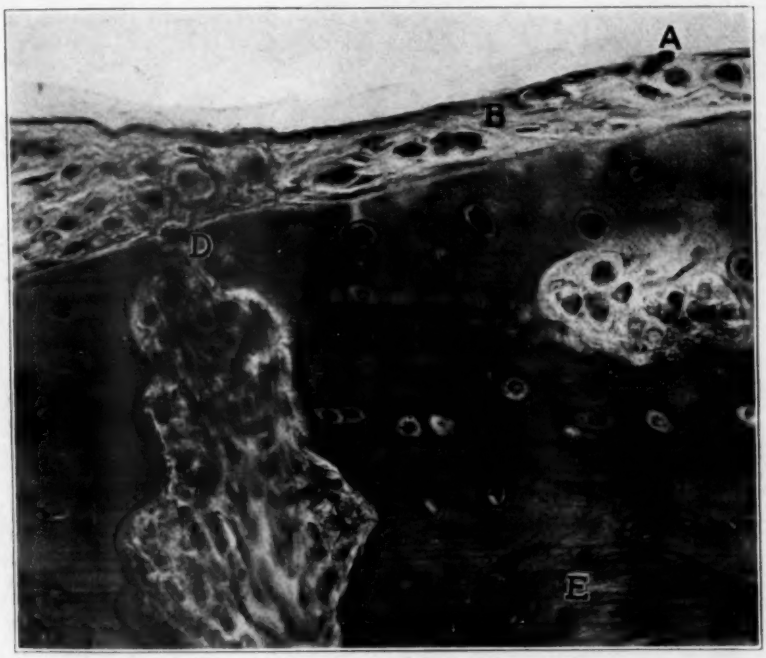

Fig. 4.—Regeneration of cartilage after four weeks in a defect through to the calcified matrix in the patella (section 7 a, under high power; area *D* in figure 3): *A*, young multinucleated cartilage cells; *B*, connective tissue fibers in new hyaline matrix; *C*, normal calcified matrix; *D*, proliferation of connective tissue from the subchondral marrow into fibrous pannus on surface; *E*, normal bone.

suggesting an early formation of fibrocartilage. The edges of the hyaline matrix adjacent to the defects were bent over and of hooklike appearance. They presented a pale-staining matrix and cells with a border showing disintegration and fibrillation. In one twelve week specimen, the bony edge of the defect showed evidence of bone repair. This margin was sharply demarcated and covered by fibrocartilage. In one four week specimen, all defects contained a moderate amount of fibrin, pus and granulation tissue, which was taken to be an evidence of infection.

This joint, grossly, contained a thick sticky exudate. Some of the sections in this joint presented areas of cartilage cells in fibrous tissue adjacent to fibrocartilage. In many sections there was a definite proliferation of connective tissue into the defects from the bone-marrow. One four week section of the upper intercondylar space showed a fibrous layer covering the defect continuous with a fibrous covering of the cartilage on both sides, which was believed to be a perichondrium. Many of the sections presented an extension of the fibrous tissue from the defect over the edge of the adjacent cartilage. There was evidence of fragmentation of the underlying bone in most of the defects, which did not take a normal stain.

Cartilage Traumatized by Direct Force.—Six joints were used in this study. After the knee had been exposed, the joint was fully flexed with the patella

Fig. 5.—Regeneration of cartilage after twelve weeks in a defect through to the subchondral bone in the internal condyle of the tibia (section 2 d, under low power): *A*, area of new hyaline cartilage showing large, multinucleated cells and light matrix; *B*, new fibrocartilage; *C*, cartilage cell columns of deep layers bending toward the defect; *D*, healed margin of calcified matrix and bone lining the defect.

dislocated to one side. The cartilage over the lower condylar ridges of the femur was then traumatized by vigorous pounding with a small metal hammer for one minute. One dog was killed in twelve weeks, three in four weeks and one in one week.

On gross examination, the cartilage over the condylar ridges of the twelve week specimen appeared to be flattened. In all of the four week specimens, the cartilage showed little or no gross evidence of trauma. The one week specimen showed evidence of trauma.

The microscopic sections from eleven specimens were satisfactory. Definite evidence of the regeneration of hyaline cartilage was present in two specimens, one of twelve weeks and one of four weeks. Nests of new cartilage cells could be demonstrated taking a deep stain on the internal ridge of a twelve week section. One border of the hyaline matrix was covered by a fibrous layer, which was thought to be perichondrium. The outer layer of hyaline cartilage showed many long spindled-shaped cartilage cells in an irregular arrangement beneath the perichondrium. These were thought to represent new cartilage cells, differentiating

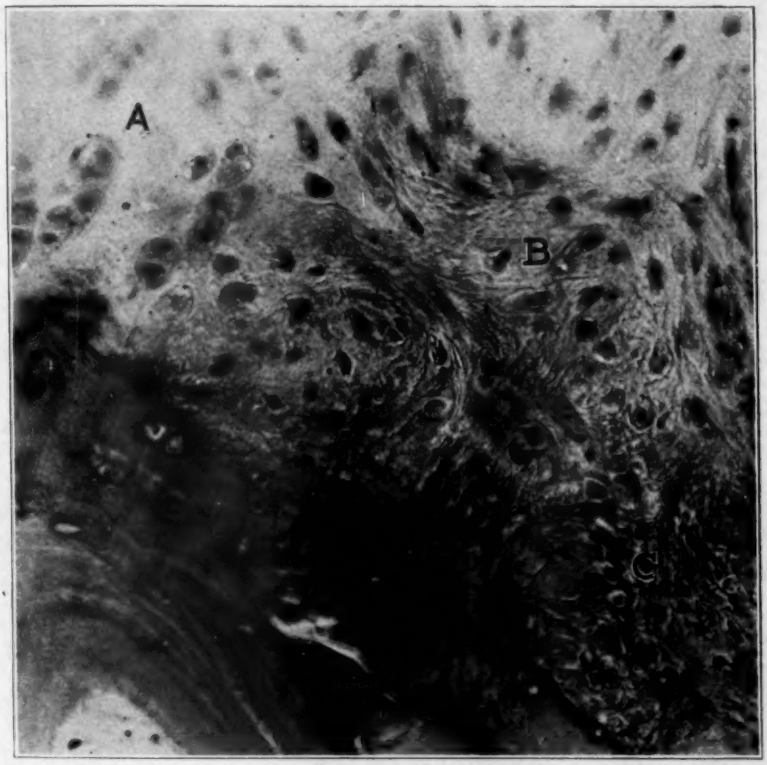

Fig. 6.—Regeneration of cartilage after twelve weeks in a defect through to the subchondral bone in the lower intercondylar space of the femur (section 3 d, under high power): *A*, large new, multinucleated cartilage cells in new, light-staining matrix; *B*, new fibrocartilage adjacent to new hyaline cartilage; *C*, cartilage cells in connective tissue (connective tissue cartilage) adjacent to new fibrocartilage.

from the perichondrium, as was shown by Haas in his costal cartilage experiments. On the internal ridge of the four week section could be seen many well stained, large new cartilage cells. In all of the sections there was observed an irregularity of the cartilage margin along the traumatized ridges with fibrillation and extremely light stained matrix. In four of the condylar ridges there were breaks in the cartilage matrix with long clefts extending obliquely down to the

calcified matrix. In two sections, the line of the calcified matrix was depressed and broken (fig. 7), and this was felt to have been caused by the trauma. Some of these clefts contained fibrin and small bits of pale-staining, disintegrating hyaline matrix, as also did some of the indentations on the surface of the ridges. The perichondrium, when present, was lifted up, and in one section red blood cells showed between this and the matrix. In two sections, there was a marked localized thickening of connective tissue, containing fibrocartilage in the form of a protrusion from the hyaline matrix. This was thought to be a reaction to the trauma. In one section, there was disintegration of the traumatized area into cartilage cells and fibrils with the formation of fibrocartilage. This was taken to be a reversion of type from hyaline cartilage to fibrocartilage. In all cases in which a perichondrium was present, this ended at the traumatized area. In

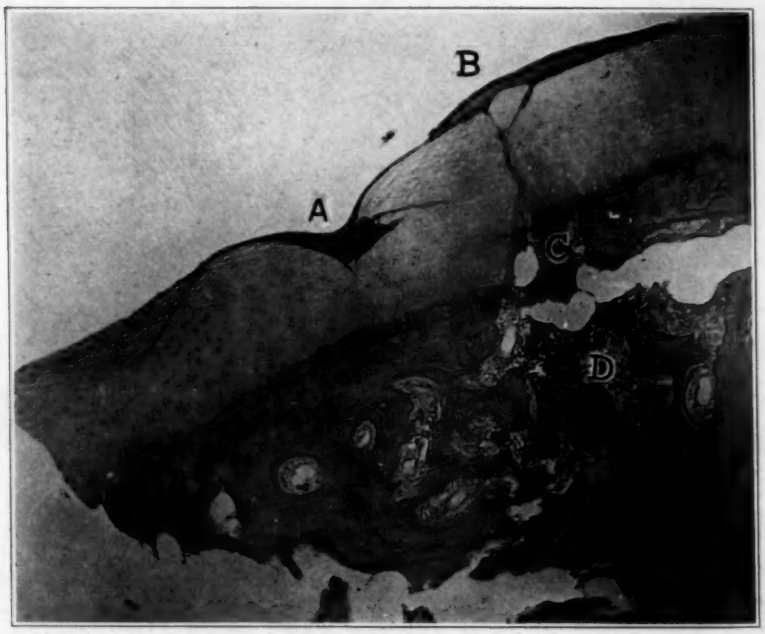

Fig. 7.—Regeneration of cartilage after one week in external condylar ridge of the femur traumatized by direct force with hammer (section 13 g, under low power): *A*, indentation of the cartilage filled with fibrin; *B*, fibrin on the surface of the cartilage with break in the matrix beneath; *C*, broken and depressed edge of calcified matrix; *D*, fragmentation of bone.

one four week specimen which showed grossly a thick exudate in the joint and was thought to be infected, the traumatized condylar ridges presented a marked depression extending into the subchondral bone. An absorption of the cartilage had occurred, and the defects were filled with well vascularized granulation tissue containing islands of pale-staining, disintegrating cartilage, pus and fibrin. The underlying bone was poorly stained and looked necrotic. Connective tissue from the bone-marrow could be seen penetrating into the spaces. The picture was so different from that seen in the other sections in this group, that the reaction was undoubtedly due to the element of infection added to the trauma.

REGENERATION IN CARTILAGE DEFECTS AFTER VARIOUS LAPSES OF TIME

After Twelve Weeks.—Eleven defects were produced in three different knee joints. In three of these, the defect was made through to the calcified matrix with a scalpel and in seven through to the subchondral bone with a burr; in one the condylar ridges of the femur were traumatized with a hammer.

On gross examination, the best evidence of healing of the defects was in the external condyle of the tibia. The defects here were made into the subchondral bone, and were filled with fibrous tissue. The next best evidence of healing was

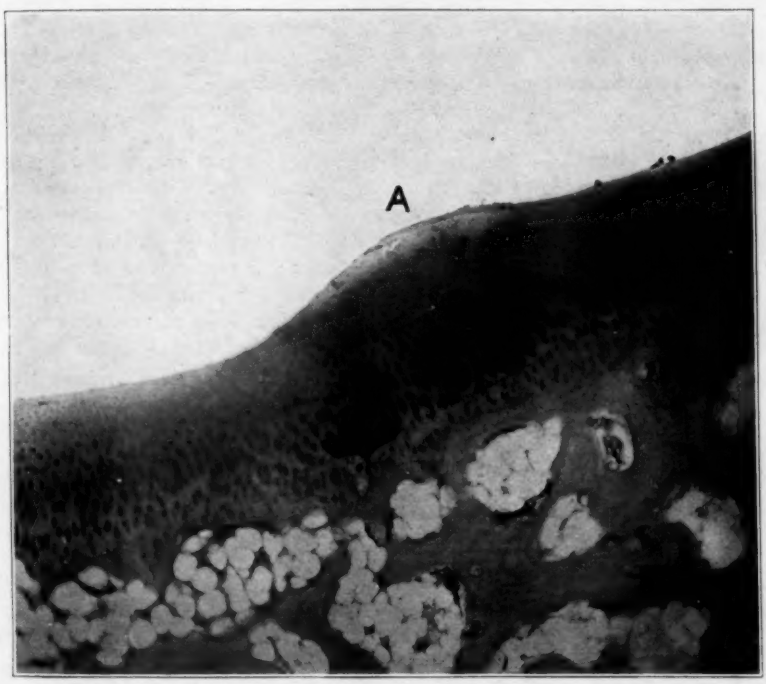

Fig. 8.—Regeneration of cartilage after twelve weeks in a defect through the superficial layers in the internal condylar ridge of the femur (section 3 b, under low power): *A*, area of hyperplasia of new cartilage cells and matrix, showing a protrusion from the cartilage edge.

in the internal condyle of the femur, where the defect had been made into the subchondral bone. There was definite evidence of healing in all of the defects examined.

The microscopic sections from ten of the eleven areas were satisfactory. In seven of the ten there was definite evidence of the formation of new hyaline cartilage. In three of these there were areas of new hyaline cartilage adjacent to new fibrocartilage which, in turn, was adjacent to areas of cartilage cells in connective tissue (fig. 6). In two sections, a proliferation of new hyaline matrix could be seen surrounding the new cartilage cells. All of the defects contained

well vascularized connective tissue. One defect made into the subchondral bone in the internal condyle of the femur was apparently lined with a well demarcated and well healed bone margin (fig. 5). There were pale-staining and disintegrating cartilage edges and cartilage nodules in the defects.

After Eight Weeks.—Ten defects were created in this study in two elbow joints and one wrist joint. In seven, the defect was through the superficial cartilage layers, and in three through to the calcified matrix.

Gross evidence of healing was present in six of the ten defects. The healing did not appear complete, and in some there was evidence of a proliferation of fibrous tissue.

The microscopic sections from all ten areas were satisfactory. In six of the ten, there was evidence of the formation of new hyaline cartilage. The best regeneration was observed in a defect through to the calcified matrix on the radial surface of the scaphoid of the wrist. In this section, along the edge of the incised hyaline matrix could be seen a lighter stained, new hyaline matrix having a fibrillar appearance, in which were contained many nests of new, irregularly placed, deeply stained, multinucleated cartilage cells. The next best area of regeneration was in a superficial defect on the head of the radius, in which new cartilage cells were found surrounded by a matrix having a fibrillar appearance. Young cartilage cells were also found in defects on the posterior surface of the humerus, on the lower end of the radius, on the head of the radius, and on the radial surface of the semilunar bone of the wrist. There were cartilage cells in a fibrous pannus in the defects on the olecranon fossa, where the cartilage is normally found to be fibrocartilage. Some fibrin and fibrous tissue were present in some defects.

After Four Weeks.—Twenty-five defects were produced in four knee joints. In eight, the defect was through the superficial cartilage layers, in four through to the calcified matrix and in six through to the subchondral bone; in six, the condylar ridges of the femur were traumatized with a hammer.

On gross examination, there was evidence of healing and repair in all of the areas. The best attempt at repair was on the external condyle of the tibia. Fibrous tissue filled some of the defects. In one knee joint, in which a moderately thick exudate suggesting an infection was found, the defects appeared to be filled with granulation tissue.

Twenty-one of the twenty-five sections studied were satisfactory. In two, there was definite evidence of the regeneration of hyaline cartilage. In one of these sections in a defect of the patella through to the calcified matrix (fig. 3), there was a marked proliferation of vascularized connective tissue from the perichondrium on one side, and in this tissue were found islands of new hyaline cartilage cells and matrix along with some old, pale-staining, disintegrating islands of hyaline cartilage. Along the incised edge of the cartilage in another portion could be seen some new hyaline matrix containing new cartilage cells. The other section showing regeneration was in the internal condylar ridge which had been traumatized with a hammer. The affected area showed a depression filled with vascularized granulation tissue, pus, fibrin and old, disintegrating, pale-staining cartilage nodules. On one border could be seen some well stained, multinucleated new cartilage cells. This section was from the joint containing the thick exudate referred to. In some of the sections there were large quadrilateral cartilage cells, previously described, which may have represented proliferating cartilage cells. In seven sections there were cartilage cells in connective tissue associated with fibrocartilage partially filling the defect. Many disintegrating old cartilage nodules

were observed in the defects. There were fibrillation and disintegration of the matrix along the edges of the defect. The fibrous pannus, when found filling the defect, showed many injected blood vessels.

After Two Weeks.—Thirteen defects were produced in four knee joints. In five, the defect was through the superficial cartilage layers, in two through to the calcified matrix and in four through to the subchondral bone; in two, the condylar ridges of the femur were traumatized with a hammer.

Gross examination revealed no evidence of healing in any of the defects.

The microscopic sections of ten of the thirteen defects were satisfactory. In only one was there any evidence of attempted cartilaginous repair. This was a section of a superficial defect on the external condyle of the tibia (fig. 1). In this section, the defect was partially filled with a loose fibrous pannus showing some blood vessels and fibrin. From one margin there had proliferated a new area of fibrocartilage, which was connected with the fibrocartilage adjacent to the hyaline cartilage on the extreme border of the joint surface. The cell columns of the deep layers of hyaline cartilage on one edge of the defect were bending toward the defect. This was shown to be the case in some of Haebler's [20] experiments with regeneration of cartilage. Four of the sections showed fibrin partially filling the defects with an occasional extravasation of leukocytes. Some of this fibrin appeared to be undergoing an organization. The incised edges of the cartilage were generally of a pale stain and showed fibrillation.

After One Week.—Fifteen defects were produced in two knee joints. In nine, the defect was through the superficial layers and in four it was through to the calcified matrix; in two, the condylar ridges were traumatized with a hammer.

Gross examination showed no evidence of healing in any of the defects.

The microscopic sections of all fifteen defects were satisfactory. There was no evidence of regeneration of cartilage in any of these sections. In four sections no changes could be noted. In one section of the external condyle of the tibia, there were some deeply stained cartilage cells on the surface which appeared to be of recent origin, but it was not thought that they represented a regenerative reaction. In four sections, the defects were partially filled with fibrin (fig. 7). The traumatized cartilage edge was faintly stained and showed some fibrillation.

REGENERATION IN CARTILAGE DEFECTS IN VARIOUS AREAS OF THE KNEE JOINT

In the Patella.—A defect was produced in eight patellae. In two, the defect was through the superficial layers, and in six it was through to the calcified matrix. Two dogs were killed in twelve weeks, three in four weeks, one in two weeks and two in one week.

Gross inspection showed evidence of healing in two of the twelve week specimens, and in one of the four week specimens.

The microscopic sections of all eight specimens were satisfactory. There was evidence of regeneration of cartilage in three. Two twelve week sections showed new cartilage cells in proliferated connective tissue, while one, in addition, showed new hyaline matrix surrounding the new cartilage cells. One four week section showed new cartilage cells in a fibrous pannus, and also new cartilage cells adjacent to new hyaline matrix along the incised cartilage edge (figs. 3 and 4). One four week section showed the defect to be filled with a fibrous pannus containing cartilage cells and fibrocartilage. The fibrous pannus was all well vascularized, and in some sections this was clearly a proliferation of the marginal perichondrium. The incised cartilage edges were faintly stained, and showed evidence of fibrillation.

In the Condyles of the Femur.—A defect was produced in eight internal condyles, and six external condyles in eight different knee joints. The defect was through the superficial layers of cartilage in six, through to the calcified matrix in two, and through to the subchondral bone in six. One dog was killed in twelve weeks, three in four weeks, two in two weeks and two in one week.

On gross examination, the most marked healing was noted in the twelve week defect of the internal condyle, which was made through to the subchondral bone. Healing was noted in all of the four week specimens. There was no difference between the healing in the external, and that in the internal condyles.

The microscopic sections of ten of the fourteen areas were satisfactory. The four unsatisfactory sections were on the outer margins of the condyles where the cartilage is normally fibrocartilage. There was no evidence of the regeneration of cartilage in any of the ten sections. Two four week sections through the superficial layers showed large quadrilateral cells on the surface of the cartilage. There were cartilage cells in well vascularized connective tissue in one twelve week section and one four week section of a defect through to the subchondral bone. Fibrin was found partially filling some of the defects. No difference could be ascertained in the power of regeneration in the two condyles.

In the Condylar Ridges of the Femur.—A defect was produced in the condylar ridges of ten knee joints. The superficial layers of cartilage were removed in three, the cartilage was incised through to the calcified matrix in one, and it was traumatized with a metal hammer for one minute in six. Two dogs were killed in twelve weeks, four in four weeks, two in two weeks and two in one week.

On gross examination, the twelve week and the four week specimens, in which the cartilage was removed with a scalpel, showed healing. Little evidence of injury could be demonstrated in the condylar ridges which had been traumatized with a hammer; however, some of these showed a flattening of the cartilage.

Sixteen microscopic sections were examined, six of which showed only the internal ridge, six only the external ridge, and four both ridges. New cartilage cells were observed in three of the sixteen sections. Three internal ridges and one external ridge showed this regeneration. One twelve week section with the defect through to the calcified matrix showed new cartilage cells adjacent to an increase in hyaline matrix with a vascularized fibrous pannus filling the defect. There were many nests of new cartilage cells seen in a twelve week section traumatized with a hammer.

In this same section were also seen spindle-shaped cartilage cells, irregularly arranged along the border, and this was thought to represent an early stage of repair. In one four week section of cartilage traumatized with a hammer, new cartilage cells were seen on one side of the defect, which was filled with a vascularized fibrous pannus, fibrin and pus cells. No striking difference was noted between the regenerative changes in condylar ridges traumatized with a hammer and those in cartilage incised with a scalpel. The changes found in the external ridges apparently were the same as those found in the internal ridges.

In the Intercondylar Spaces of the Femur.—A defect was produced in four upper intercondylar spaces and in six lower intercondylar spaces in eight knee joints. The defect was through the superficial layers of cartilage in one, through to the calcified matrix in three, and through to the subchondral bone in six. Two dogs were killed in twelve weeks, three in four weeks, one in two weeks and two in one week.

Gross evidence of healing was found in all of the twelve week and four week specimens. In two four week specimens, granulation tissue filled the defect.

The microscopic sections from all ten specimens were satisfactory. In only one twelve week section of a defect in the lower intercondylar space through to the subchondral bone was there any evidence of new cartilage cells (fig. 6). This was adjacent to a vascularized fibrous pannus containing cartilage cells and some new fibrocartilage. There were pale-staining, degenerating nodules of hyaline cartilage in this defect. Six of the other nine sections showed cartilage cells either in a fibrous pannus alone or associated with fibrocartilage. A great many of the disintegrating islands of hyaline cartilage were also seen. No difference was noted between the regenerative changes of the upper and those of the lower intercondylar spaces.

In the Condyles of the Tibia.—A defect was produced in seven internal condyles and eight external condyles in eight knee joints. The defect was through the superficial cartilage layers in nine, through to the calcified matrix in one, and through into the subchondral bone in five. Two dogs were killed in twelve weeks, two in four weeks, two in two weeks and two in one week.

On gross examination, the greatest amount of healing was seen in the external condyles. This healing was more marked than that in any of the other areas of the knee joint. There was no healing observed in less than four weeks. In some defects there was a fibrous pannus.

The microscopic sections of eleven of the fifteen specimens were satisfactory. There was evidence of the regeneration of cartilage in two twelve week sections with the defect through to the subchondral bone (fig. 5). These showed new cartilage cells with a large amount of fibrocartilage adjacent. A well vascularized fibrous pannus filled one defect, which was lined by a margin of healed bone. In one superficial defect of a two week section of the external condyle there was evidence of early regeneration (fig. 1). Some sections showed cartilage cells in fibrous tissue partially filling the defect. The margins of the hyaline matrix were faintly stained and presented evidence of fibrillation.

In the Perichondrium.—In the earlier periods there was always an element of doubt as to whether articular cartilage was completely covered by an extension of the synovial membrane called perichondrium. Hunter [2] spoke of demonstrating the perichondrium only with great difficulty and finding that it was adherent. Henle [26] said that the epithelium was continued in a thinner layer on the articular surfaces of the cartilage, on which it was separated from the cartilage corpuscles by a thin layer of cellular tissue. Toynbee [27] wrote that the free surface of articular cartilage was covered by synovial membrane, to which it was attached by a cellular areolar-like tissue. The membrane from the central part of the cartilage showed scarcely any appearance of areolar tissue, being translucent and nearly homogeneous in structure. Soem-

26. Henle, F. G. J.: Muller's Arch., 1838, p. 116.

27. Toynbee, Joseph: Researches Tending to Prove the Non-Vascularity and the Peculiar Uniform Mode of Organization and Nutrition of Certain Animal Tissue, etc., Philosophical Transactions of the Royal Society, London, 1841, pt. 1, pp. 159-192; On the Structure of Synovial Membrane Covering the Surface of Adult Articular Cartilage, London J. M. **1**:217, 1849.

mering [28] and Bichat [29] also felt that the synovial membrane covered the surface of the articular cartilage. Brodie [30] agreed with Bichat and stated that where the synovial membrane was reflected over the articular cartilage it was thin and readily torn, but its existence might always be distinctly demonstrated by careful dissection.

Leidy,[3] Todd and Bowman [31] and Ogston [9] of the earlier writers were of the opinion that the synovial membrane covered only the margin of the articular cartilage for a short distance. Leidy wrote that it was present in the fetal state over the whole of the articular cartilage, but that after birth it was progressively destroyed from the center to the circumference by pressure and attrition. Magendie,[32] Velpeau [33] and Cruveilhier [34] were of the same opinion. Fisher [35] wrote that the central area of the articular cartilage had no perichondrium. The superficial stratum consisted of flattened cells arranged in groups parallel to the surface. The immediate surface was formed of the matrix. This superficial layer showed no signs of degeneracy or diminished vitality. He further stated that the lateral area of articular cartilage was covered by a delicate extension of the synovial membrane, which toward the center was a close set layer of endothelial cells, which subsequently produced hyaline matrix. Davis,[36] Strangeways,[37] and Ito [19] stated that there was no membrane on articular cartilage. In the textbooks on anatomy of Gray [38] and of Schäfer,[39] it is written that the articular

28. Soemmering, S. T.: De Corporis Humani Fabrica, Traj. ad Moenum, sumpt. Varrentrappii et Wenniri, 1794-1801.

29. Bichat, M. F. X.: Organization du systeme cartilagineux, anatomie générale appliquée à la physiologie et la médicine, Paris, 1802.

30. Brodie, Sir Benjamin C.: Pathological and Surgical Observations on the Diseases of the Joints, ed. 3, London, 1836, p. 7.

31. Todd, R. B., and Bowman, William: The Physiological Anatomy and Physiology of Man, London, 1856, vol. 1, p. 88.

32. Magendie, Francois: A Summary of Physiology, translated from the French, Baltimore, E. J. Coale & Company, 1822.

33. Velpeau, A. L. M.: A Treatise on Surgical Anatomy or the Anatomy of Regions Considered in Its Relation with Surgery, translated from the French by J. W. Stirling, New York, S. Wood & Sons, 1830.

34. Cruveilhier, Jean: The Anatomy of the Human Body, American ed. 1, translated from the last Paris edition, New York, Harper & Brothers, 1844.

35. Fisher, A. G. T.: A Study of Loose Bodies Composed of Cartilage or of Cartilage and Bone Occurring in Joints, with Special Reference to Their Pathology and Etiology, Brit. J. Surg. **8**:493, 1920-1921.

36. Davis, J. S.: The Transplantation of Rib Cartilage into Pedunculated Skin Flaps, An Experimental Study, Bull. Johns Hopkins Hosp. **24**:164, 1913.

37. Strangeways, T. S. P.: Observation on the Nutrition of Articular Cartilage, Brit. M. J. **1**:661 (May 15) 1920.

38. Gray, Henry: Anatomy of the Human Body, ed. 20, edited by Warren H. Lewis, Philadelphia, Lea & Febiger, 1918.

39. Schäfer, E. A.: Essentials of Histology, London, Longmans, Green & Company, 1916.

cartilage is covered by synovial membrane, except where the opposed articular ends of bones are exposed to friction.

With the study of the sections for regenerative changes in cartilage, a careful search was made for evidence of a fibrocellular layer similar to the synovial membrane covering the articular cartilage, which might be called a perichondrium. When this was found to be present, an attempt was made to determine whether this perichondrium played any part in the formation of the reparative tissue. Of the seventy-four sections, fifty-nine were satisfactory for determining the presence or absence of a perichondrium. Four of the fifty-nine showed evidence of a perichondrium across all or most of the cartilage border:

1. Over one external condyle of the tibia, which was adjacent to the posterior margin of the cartilage, there was a definite thin fibrous membrane covering the whole edge of the cartilage matrix, which, however, became thinner towards the center. Elongated branching cells were present on the cartilage side of this layer. These cells were separate and distinct from the superficial cartilage cells. In one place, this membrane was stripped back from the underlying cartilage, and showed clearly the fibrillar and cellular structure.

2. There was a thin fibrous membrane over both condylar ridges in a twelve week section of cartilage traumatized with a hammer. In the intercondylar space there was a ligamentous attachment, which was thought to be the attachment of a crucial ligament. The fibrous layer over the cartilage in this section might have been a reaction to the trauma or an extension from the adjoining ligament, and might not have represented a true perichondrium continuous with the synovial membrane. Seggel [14] said that when the defect lay close to the insertion of a crucial ligament there was a secondary connective tissue pannus proliferated over the cartilage, which might explain the fibrous layer over the cartilage in this section.

3. In a four week section of the external condylar ridge traumatized with a hammer, a fibrous layer could be seen covering the cartilage on both sides of the ridge, but not over the maximum point. The possibility here is that the fibrous layer represented a true perichondrium but had not been exposed to pressure and friction.

4. In a four week section of the upper intercondylar region, in which the defect was made through to the subchondral bone, there could be seen a dark staining fibrous layer, containing long spindle cells, extending over all of the cartilage margin and defect, which apparently was in no way connected with the underlying cartilage or the connective tissue filling the defect. The cartilage in this section was in the uppermost portion of the intercondylar space close to the margin of the joint, and again had probably not been exposed to friction and pressure.

In twenty-six, or 47 per cent, of the remaining fifty-five sections a perichondrium could be demonstrated over the outer margin of the cartilage. When the defect was close to this margin, there was a proliferation of fibrous tissue of the perichondrium into the defect. Thus, the perichondrium was here taking a definite part in the regeneration. Many of the injured joint areas were not adjacent to the cartilage edges, so that an evidence of a marginal perichondrium would not be looked for. The superficial margin of the cartilage took an extremely dark stain in sixteen, or 29 per cent, of the fifty-five sections. In

places, the most superficial, nonnucleated layer of the cartilage was stripped up, and it could easily be seen how this might be mistaken for a perichondrium. The fibrous tissue, filling the defect in its outer portion, had proliferated for a short distance over the adjacent edge of the cartilage in seven, or 13 per cent, of the fifty-five sections.

In conclusion of this part on the perichondrium, it can be stated that the articular cartilage studied presented a perichondrium only over the margins of the articular edges and in those areas not exposed to pressure and friction. There was evidence of this perichondrium's taking a definite part in the regenerative changes of the cartilage in the lateral defects but not in the central defects.

COMMENT

Macroscopic evidence of healing is not to be noted in the defects of specimens before four weeks. After four weeks or more, the defects showing any reparative changes look as if they have been filled with fibrous tissue. No one of these is covered by tissue having the normal glistening appearance of cartilage. In some specimens, especially in those in which a sticky exudate is present in the joint, the tissue filling the defects looks like granulation tissue. The best gross evidence of repair is in the external condyle of the tibia. The only explanation of this observation is that either the defects have been made close to the margin of the cartilage, or there has been an increased stimulation to effusion of fibrin followed by organization and the formation of connective tissue, owing to the better circulation in the articular vascular circle or in the capillary convolutions of the subchondral bone adjacent to this region of the knee.

Most of the previously reported experimental work has been concerned with the regeneration of cartilage in defects made through to the subchondral bone. There are few references to the regeneration of the superficial layers of cartilage. The results of my experiments show that when the defects are made only in the superficial layers of cartilage, five of the seven eight week specimens show regeneration, as manifested by the presence of new, large, multinucleated cartilage cells. The head of the radius stands out as the area in the elbow and wrist with the most complete regenerative changes. In three of the eight four week specimens, there are some large, distended-looking, quadrilateral cartilage cells. It is thought that these are playing some part in the reparative changes. The same type of cells was described by Pennisi (1904).[40] One two week section shows a turning of the lines of axis

40. Pennisi, A.: Sul processo di quarigione delle ferite delle cartilagini, Policlinico (sez. chir.) **11**:489, 1904.

of the cell columns in the deeper layers of the cartilage toward the defect (fig. 1). This is shown beautifully in some of the photomicrographs in Haebler's [20] work on the regeneration of cartilage. The observations in this study, namely, that in the superficial defects after eight weeks a moderate degree of regeneration of the hyaline cartilage is present and that after two weeks a great many early microscopic evidences of repair are to be seen, do not agree with those of Seggel,[14] Fisher,[35] Ciociolo [17] and Haebler.[20] Some of the defects contain fibrin, and some contain fibrin showing evidence of organization. In one four week section of the internal condyle of the tibia (fig. 2) there is a proliferation of fibrous tissue in the defect. The fibrous tissue has spindle cells in the superficial portion and oval cells in the deep part resembling cartilage cells. It penetrates, in two places, the pale-staining, irregular hyaline cartilage border. This confirms an observation of Redfern.[1] All of these manifestations of attempted repair are conclusive evidence that there is regeneration of cartilage in superficial defects with no involvement of the underlying bone.

The cartilage defects made through to the calcified matrix show slightly more pronounced regenerative changes than the more superficial defects. All of the twelve week sections, one eight week section, and one four week section (fig. 3) show large, new, multinucleated cartilage cells. Some of the defects are partially filled with connective tissue containing cartilage cells. These cartilage cells are thought to have been extruded from the adjoining cut edge of the cartilage. This is the cartilaginous callus described by Fisher [35] and others.

The cartilage defects made through to the subchondral bone show the most complete evidences of cartilage repair. All of the twelve week sections (figs. 5 and 6) show excellently the transitional stage from cartilage cells in connective tissue (connective tissue cartilage) to fibrocartilage to new areas of hyaline cartilage containing the large multinucleated, deep-staining, cartilage cells. Most of the four week sections show the connective tissue cartilage and fibrocartilage, but do not show new areas of hyaline cartilage. Unfortunately, there are no sections between twelve and four weeks involving the subchondral bone. Schmidt (1923)[41] showed the presence of this connective tissue cartilage after eighteen days, and also a beginning proliferation of new cartilage cells. Many of the sections show the subchondral marrow playing a part in the regeneration. This is accomplished by the proliferation of connective tissue into the defect. Such connective tissue takes part in the formation of connective tissue cartilage. This was shown by Tizzoni,[11] Rimann [16] and Ito.[19] Many disintegrating pale-staining cartilage islands are

41. Schmidt, A.: Experimentelle Untersuchungen über das Schicksal teilweise ausgeloster Knorpelknochenlappen von der Gelenkflache des Kniegelenkes, Beitr. z. klin. Chir. **130**:142, 1923-1924.

observed, surrounded by and intimately connected with fibrous tissue. The margins of the cartilage adjacent to the defects all show various degrees of fibrillation and disintegration, and are very lightly stained. In some of these areas of disintegration there are areas of regeneration with new cartilage cells and new matrix. This was observed by Gies.[13]

The cartilage traumatized by pounding with a metal hammer shows definite regenerative changes. Large new cartilage cells are seen on the internal condylar ridge of one twelve week section and one four week section. These new cells are never found in the superficial layers of cartilage, but are in the adjoining layers. In some sections there is an increase of hyaline matrix about these cells. The margin of the cartilage is generally faintly stained and presents a disintegrating border with small cartilage cells. In my experiments, all of these new areas of cartilage formation are well circumscribed. Seggel[14] mentioned this fact. Fisher,[35] after traumatizing cartilage for two minutes with a hammer, found no change after five weeks. This is not in accord with my observations. Many of the sections show clefts in the cartilage due to the trauma. These clefts are filled with pale-staining, disintegrating cartilage nodules and fibrin undergoing organization into granulation tissue. In two sections, a localized connective tissue thickening is present over the maximum point of the ridge, which contains fibrocartilage. This is undoubtedly a reaction to the trauma. The specimen of a knee filled with a thick sticky exudate, suggesting an infection, shows a similarity to the experimental case of Fisher,[35] in which he injected *Streptococcus salivarius* in broth culture into a knee previously traumatized with a hammer. He found that the knee was filled with creamy pus, that the synovial membrane was converted into granulation tissue, and that there was some absorption of the articular cartilage. In my specimen there was complete absorption of the articular cartilage over the traumatized area with a proliferation of granulation tissue, pus and fibrin in the absorbed area.

The element of time required to show different types of regenerative changes in the cartilage has produced some interesting observations. The earliest microscopic evidence of repair is the fibrin formation, which is seen as early as one week (fig. 7). After two weeks in some of the sections there is definite evidence of the organization of fibrin and of the occurrence of granulation tissue (fig. 1). These observations are mentioned by a great many investigators. The granulation tissue is then observed to change into connective tissue, which is found in the four week sections (fig. 2). In one third of the four week sections, cartilage cells are present in connective tissue and fibrocartilage. There is also seen a disintegration of bits of old, pale-staining cartilage into connective tissue, which then undergoes changes into connective tissue cartilage and fibrocartilage. It is interesting to note from the work of

Marchand [21] that the changes in perichondrium covered cartilage are essentially the same as those I found in articular cartilage. There are definite evidences of new cartilage cells in 70 per cent of the twelve week sections, 60 per cent of the eight week sections, and 10 per cent of the four week sections. No new cartilage cells are seen in less than four weeks; however, in one two week section (fig. 1) there is a bending of the cell columns of the deep layers of the cartilage toward the defect with an area of new fibrocartilage. Many of the four week and eight week sections showing new cartilage cells on the margin of the hyaline matrix (fig. 3) show a proliferation of new, finely fibrillar hyaline martix about these new cells. This new matrix apparently has been formed by the new cartilage cells themselves. This was observed by Haebler [20] in superficial defects after 225 days.

The comparative study of regeneration in different areas of the knee joint has not disclosed any one area which has greater regenerative powers than the others. Probably the best pictures of regeneration are to be seen along the denuded margins of the patella (fig. 3). A proliferation of fibrous tissue from the adjacent synovial membrane seems to play a large part. In three sections of the patella, new areas of hyaline cartilage are to be seen in connective tissue, which is adjacent to connective tissue cartilage. In another section of the patella, fibrocartilage is observed with connective tissue cartilage, but no new hyaline cartilage is seen. The condylar ridges of the femur have presented nests of new cartilage cells in three sections (fig. 8). The internal ridge has been the most frequently affected. These condylar ridges, however, do not show the cartilaginous callus. There are not sufficient microscopic sections of the condyles of the tibia to confirm the gross observations, namely, that the best evidence of repair is to be found in the defects in the external condyle of the tibia. Two of the tibial sections show new cartilage cells in twelve weeks, while one two week section shows early changes but no new cartilage cells. In the defects in the condyles of the femur and intercondylar spaces, there are many evidences of cartilaginous callus, but only one section shows new, multinucleated cartilage cells.

Haebler [20] found that after placing the legs of dogs in plaster following the creation of defects in the cartilage, there was a definite disturbance of healing in the defects. In my experiments, all of the joints were placed in plaster immediately after the operation, and the plaster was allowed to remain on from one to two weeks. The casts were then removed, and the dog was allowed to move the joint. The fact that the joints were immobilized for this short time and the normal physiology of the joints disturbed, may have had an effect on the degree and amount of regeneration in the cartilage defects.

SUMMARY AND CONCLUSIONS

Experiments have been performed on the joints of fourteen dogs in order that a study might be made of the regeneration of the hyaline cartilage in superficial and deep defects, and of the reaction of this cartilage to direct trauma. These dogs were killed in from one to twelve weeks after the injuries to the cartilage. The more important contributions in the literature on this subject have been reviewed and correlated with the observations reported here.

The results of these studies show that hyaline cartilage in joints does not regenerate in less than four weeks. The best evidences of regeneration are found in twelve weeks.

In these regenerative changes the following tissues have been observed to appear: first, fibrin; second, granulation tissue; third, connective tissue; fourth, cartilage cells in connective tissue (connective tissue cartilage); fifth, fibrocartilage, and sixth, new hyaline cartilage.

Regeneration of hyaline cartilage has been found in superficial defects not involving the subchondral bone. The greatest amount of regeneration, however, is seen in those deep defects which do involve the subchondral bone.

Hyaline cartilage is observed to react occasionally to direct trauma with a proliferation of nests of new cartilage cells.

No striking difference in the regenerative powers of cartilage in different areas of the knee joint can be demonstrated.

No definite evidence of a perichondrium covering the articulating surfaces of hyaline cartilage has been observed.

In these experimental studies there was enough evidence of hyperplasia of cartilage as a result of injury and trauma to justify further experimentation.

PROTOCOL OF EXPERIMENTS

EXPERIMENT 1.—The knee joint was used, and the defects were made with a burr through to the subchondral bone in the internal condyle of the femur and the external condyle of the tibia. The dog was killed twelve weeks after the operation.

Internal Condyle of the Femur.—On gross examination, the defect could be clearly seen and showed evidence of healing. The microscopic section was cut through the center of the defect. This center was filled with a well-vascularized fibrous pannus. At one edge in the fibrous tissue were cartilage cells which appeared to have arisen from the deeper layers of the adjacent cartilage. This fibrous tissue at one edge extended over the cut edge of the cartilage. The cartilage cells and the matrix were faintly stained along the edges and the matrix showed beginning disintegration. There was a hooklike projection of old cartilage into the fibrous pannus at one edge. When the defect was being created with the burr, the cartilage most likely bent in at this point before breaking. Over part of the defect extended a fibrocellular membrane with elongated fusiform cells, which was suggestive of a perichondrium. Outside the fibrous pannus lay several nodules of bone and cartilage, which were pale-staining and showed evidence of disintegration.

External Condyle of the Tibia.—On gross examination, almost complete healing was evident, the defect being recognized with difficulty. The microscopic section was not cut through the traumatized area. Over the whole cartilage area extended a thin fibrous membrane with fusiform cells, which became thicker toward the margins. On the cartilage side of this, branching cells were seen. These were distinct and separate from the uppermost cartilage cells. In one place, this membrane had been stripped back and showed beautifully the fibrillar structure and cells. This was believed to be perichondrium.

EXPERIMENT 2.—The knee joint was used, and defects were made with a scalpel and a burr in the patella, the condyles of the tibia and the lower intercondylar space of the femur. The condylar ridges of the femur were traumatized with a hammer. The dog was killed twelve weeks after the operation.

Patella.—The defect extended through to the calcified matrix. On gross examination, the surface of the patella was beginning to look smooth. The microscopic section was cut through the center of the defect. From the synovial membrane on one margin, there was a proliferation of connective tissue, which extended over a large part of the defect. In the central portions of this, cartilage cells were seen, with early formation of hyaline matrix. The cells were larger and looked more immature toward the growing edge. The connective tissue was well filled with blood vessels. Along the margin of the incised hyaline matrix in another portion of the defect, there were well demarcated areas of new hyaline matrix, which contained well stained, large new cartilage cells. Over one side of the cartilage for a short distance was a thin fibrous membrane with blood vessels, which was believed to be perichondrium.

Condylar Ridges of the Femur.—The cartilage was traumatized with a hammer. Gross examination showed the cartilage over the ridges to be somewhat flattened, but otherwise normal. The microscopic section was clearly cut through the traumatized areas. The edges of the matrix over the ridges were faintly stained and showed disintegration and fibrillation. In the internal ridge were many large nests of new cartilage cells with well stained nuclei. These were not found in the superficial layers of cartilage but in the adjoining layers. The cartilage cells along some of the borders of the defect were spindle-shaped and had no regularity of arrangement. A fibrillar membrane containing fusiform cells covered most of the cartilage area, being absent over only one small area of the ridge. This was continuous with the ligament attached in the intercondylar space, which was thought to be a crucial ligament.

Lower Intercondylar Space.—The defect extended through to the subchondral bone. Gross examination showed that the defect was well filled with fibrous tissue. The microscopic section was cut through the center of the defect. This was well filled with a vascularized fibrous pannus with some disintegrating bone nodules on the surface. On the edges of the defect was a fibrillation of pale-staining cartilage, which was adjacent to fibrous tissue containing cartilage cells. The fibrous tissue filling the defect extended over the cartilage on one edge. The synovial membrane extended over the cartilage for a short distance on one side. Away from the defect, a break in the cartilage through to the bone-marrow could be seen, and this cleft was partially filled with vascularized connective tissue which had proliferated from the subchondral marrow.

Internal Condyle of the Tibia.—The defect extended through to the subchondral bone (fig. 5). On gross examination, there was definite evidence of fibrous tissue filling the defect. The microscopic section passed through the center of the defect. The defect was well filled with a vascularized fibrous pannus, and on

both sides could be clearly seen many nests of new, deeply stained cartilage cells adjacent to fibrocartilage, which covered the whole inner margin of the defect. The inner margin of the defect had a well healed calcified margin. In the outer portion of the defect, there was an island of disintegrating cartilage adjacent to fibrocartilage. The old cartilage had the appearance of disintegrating into fibrous tissue and then forming fibrocartilage. There was a fibrillation of the outer margin of the original cartilage with a pale stain. The fibrous tissue from the defect was growing over one edge of the cartilage.

External Condyle of the Tibia.—The defect extended through to the subchondral bone. On gross examination, it was seen that fibrous tissue filled the defect. The evidence of repair was much more marked than that seen in the defect on the internal condyle of the tibia. The microscopic section showed only one edge of the defect. The edge of the hyaline matrix was pale-staining and disintegrating, and showed an adjacent area of fibrocartilage between this and the bone. In the hyaline matrix were some irregularly shaped cartilage cells containing many nuclei, which were thought to be new cells. Between these new cells fibrils could be seen. Many blood vessels were present in the neighboring fibrous pannus. In the connective tissue about the fibrocartilage were many cartilage cells. For a short distance from the defect there was a proliferation of fibrous tissue over the cartilage edge.

EXPERIMENT 3.—The knee joint was used, and the defects were made with a scalpel and a burr in the patella, the condylar ridges and the upper and lower intercondylar spaces. The dog was killed twelve weeks after the operation.

Patella.—The defect extended through to the calcified matrix. Gross examination revealed evidence of healing. The microscopic sections showed a breaking away of cartilage, in places, from the bone along the line of calcification. The defect was not filled with any tissue. From one margin of the cartilage, the synovial membrane, which contained some spindle cells, had extended over the hyaline matrix for a short distance. Along this surface of the cartilage there were some deeply stained, new, multinucleated cartilage cells. On one side, the matrix and the cells were pale-staining, and the edge of the matrix looked frayed.

Condylar Ridges.—The defect was made through to the calcified matrix (fig. 8). Gross inspection showed evidence of healing, but the external ridge looked irregular. The microscopic section passed through both defects. The defects were filled with a vascularized fibrous tissue pannus, containing no cartilage cells. On the internal ridge, in the outer zone of the cartilage were new, deeply stained, irregularly arranged cartilage cells. The hyaline matrix projected over this area. The same new cells, in fewer numbers, were present on the external ridge. Some of the cartilage cells adjacent to the defects had a pale stain, and the matrix showed fibrillation. In spots on the surface there was a dark-staining, nonnucleated layer of cartilage which was thought to be only an outer layer of cartilage.

Upper Intercondylar Space.—The defect extended through to the subchondral bone. Gross inspection revealed evidence of healing. The microscopic section was poor. The defect was filled with well vascularized fibrous tissue and granulation tissue. The edge of the bone around the defect was well demarcated and well healed. Some giant cells were seen around the edges of the bone. Along some of the borders were a few large cells in fibrous tissue, which looked like cartilage cells.

Lower Intercondylar Space.—The defect extended through to the subchondral bone (fig. 6). Gross examination showed evidence of healing. The microscopic

section passed through the defect, which was filled with fibrous tissue and granulation tissue with many blood vessels. On one margin of the cartilage, the cell columns in the deeper layers bent their lines of axis toward the defect, adjacent to which were many large, deeply stained new cartilage cells. Fibrocartilage was contiguous with these new cells, and connective tissue containing cartilage cells was next to this. On the outer edge of the cartilage, close to the new cells was pale-staining, disintegrating matrix. Along the borders of the defect were two old cartilage islands showing disintegration. The fibrous tissue from the defect had extended over the edge of the cartilage for a short distance.

EXPERIMENT 4.—The elbow joint was used, and the defects were made with a scalpel in the head of the radius, the olecranon fossa of the ulna and the posterior surface of the humerus. The dog was killed eight weeks after the operation.

Head of the Radius.—The defect extended through to the superficial layers. It showed macroscopic evidence of healing. The microscopic section showed hyaline cartilage on three sides of bone. The defect could be clearly ascertained. About one corner of this were deep-stained cartilage cells with many nuclei intermingled with more lightly stained cartilage cells. The former were thought to represent new cartilage cells. The edges of the cartilage showed disintegration and fibrillation with an irregular border and some débris attached. The superficial layer in spots showed deep staining and was nonnucleated. Over the hyaline cartilage for a short distance, on one side, there was an extension of the fibrous covering of the normal fibrocartilage. This was the only evidence of a perichondrium.

Olecranon Fossa of the Ulna.—The defect extended through to the calcified matrix. Macroscopically, it showed definite evidence of healing. The microscopic section showed the olecranon fossa to be covered on both margins with hyaline cartilage, but the main portion of the indentation was covered with fibrous tissue containing some cartilage cells. The bone was extremely compact and contained little or no marrow cavity. Along the margin of the bone were many giant cells. On the margin of the cartilage were the capsules of cartilage cells which have been emptied of their nuclei. Covering part of the hyaline cartilage was a small area of fibrous tissue with fusiform cells going into a deep-staining, nonnucleated superficial layer of cartilage. This was the only evidence of a perichondrium. In the hyaline matrix adjacent to the fibrous covering were several deeply stained, branching cartilage cells, which it was thought might be embryonic cartilage cells.

Posterior Lower End of Humerus.—The defect extended through the superficial layers. Gross examination revealed evidences of healing. The microscopic section showed the defect clearly. In the defect, loose connective tissue was found with some deep-staining, branching cells, which were taken to be embryonic cartilage cells. Between the connective tissue and the normal hyaline matrix was a lighter staining area of hyaline matrix. This may have been new matrix. On one margin could be traced for a short distance a fibrous layer which extended from the synovial membrane. This was the only evidence of a perichondrium. There was a deep-staining, nonnucleated border of cartilage to most of the matrix.

EXPERIMENT 5.—The elbow joint was used, and the defects were made with the scalpel in the head of the radius, the olecranon fossa of the ulna, and the external and internal condyles of the humerus. The dog was killed eight weeks after the operation.

Head of the Radius.—The defect extended through the superficial layers. No macroscopic examination was made. The microscopic section showed the denuded area. Over this defect extended a fibrous layer from the cartilage edge. The superficial portion of the cartilage showed an increased number of cartilage cells,

which were deeply stained and irregularly placed, and between which in places were fibrils. The adjacent hyaline matrix was faintly stained. A few blood vessels were found in this new cartilage structure.

Olecranon Fossa of the Ulna.—The defect extended through to the calcified matrix. Macroscopic examination was not made. The microscopic section showed the indentation of the fossa, which was filled with fibrous and granulation tissue. In the fibrous tissue, adjacent to the bone, were some cartilage cells. Hyaline cartilage was not present. It is the impression after studying this section and the other one of the olecranon fossa that the bone here was normally covered with fibrocartilage.

External Condyle of the Humerus.—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed the depression in the cartilage. In this defect no fibrin or connective tissue was present. There was an extension of a fibrous membrane from the synovia for a short distance over the cartilage. This was the only evidence of a perichondrium. Some lighter staining, wavy areas ran longitudinally through the hyaline matrix beneath the incised area; these were thought to be artefacts.

Internal Condyle of the Humerus.—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed the defect clearly. The margin of this was irregular and covered with fibrin and débris. In the cartilage beneath, some elongated cartilage cells were present, but no new cartilage cells. In places, the margin of the cartilage was deeply stained and had been detached. The only evidence of a perichondrium was shown on one edge, where the fibrous tissue had extended for a short distance over the cartilage.

EXPERIMENT 6.—The wrist joint was used, and the defects were made with a scalpel in the scaphoid bone, the semilunar bone and the lower end of the radius. The dog was killed eight weeks after the operation.

Scaphoid Bone.—The defect extended through to the calcified matrix. There was macroscopic evidence of healing. The microscopic section was clearly cut through the defect. A layer of light-staining, hyaline matrix containing fibrils was superimposed on the normal-staining matrix over the extent of the incised area. Contained within this layer of lighter matrix, in places, were large, new, deeply stained, multinucleated cartilage cells. Some of the nuclei in these showed beautiful mitosis and division. Some of the new cartilage cells could be seen proliferating from the superficial cartilage cells. The edge of the matrix was fairly regular. Over the marginal edges of the hyaline matrix was a fibrous membrane, which was the only evidence of a perichondrium.

Semilunar Bone.—The defect extended through the superficial layers. There was macroscopic evidence of healing. The microscopic section showed an irregular border to the incised area. Along the margin of the matrix in the defect were many large, deeply stained, multinucleated cartilage cells. These were irregularly placed and were believed to represent a regeneration of cartilage. Along the margin of the cartilage were many elongated cartilage cells. Hyaline cartilage was on two sides of the bone, with fibrous and connective tissue on a third side. There was no evidence of a perichondrium.

Lower End of the Radius.—The defect extended through the superficial layers. There was gross evidence of healing. The microscopic section showed a deposit of fibrin and débris on the surface of the defect. In this fibrin were some large round cells which were similar to types of cartilage cells. Along the surface

were many multinucleated, irregularly placed cartilage cells which did not take a deep stain. These were new cartilage cells. There was a transverse break in the whole of the cartilage matrix in the middle of the incised area. There is a deep-staining, nonnucleated, superficial layer of cartilage, which in places had been stripped back and was broken. At both marginal edges, the fibrous tissue extended for a short distance over the cartilage and was continuous with this darkly stained superficial layer. This was the only evidence of a perichondrium.

EXPERIMENT 7.—The knee joint was used, and the defects were made with the knife in the patella, and with the burr in the upper intercondylar space and the internal condyle of the femur. The condylar ridges of the femur were traumatized with the metal hammer. The dog was killed four weeks after the operation.

Patella.—The defect extended through to the calcified matrix (figs. 3 and 4). Macroscopic examination was not made. The microscopic section showed the incised area clearly. Over about one half of the defect there was a proliferation of connective tissue, which had come from the synovial membrane covering the outer margin of one edge of the hyaline cartilage. This connective tissue pannus was thickest toward the center of the defect and gradually became thinner as the edge of the defect was approached. It contained small islands of new hyaline matrix with new, deeply stained, multinucleated cartilage cells. Adjacent to these were cartilage cells in connective tissue (connective tissue cartilage). Also contained in this fibrous pannus were small islands of old cartilage undergoing fibrillation and disintegration, with faint cell nuclei. The connective tissue was closely adherent to these islands of old cartilage. Small bits of broken off calcified matrix were observed in the connective tissue pannus. Along the incised border of the hyaline matrix not covered with the connective tissue, there were large, new, multinucleated cartilage cells surrounded by new, pale-staining matrix. These cells appeared to have arisen from the cartilage cells in the superficial layers. The mitoses of the cell nuclei could be seen. Blood vessels were present in the connective tissue pannus.

Upper Intercondylar Space of the Femur.—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section passed through the center of the defect. The defect was filled with a connective tissue pannus, which was well vascularized. The pannus was thicker and denser toward the surface of the defect. In the lower portion toward the bone there were rather large, circumscribed spaces filled with blood. In the pannus were a few pale-staining, disintegrating islands of old cartilage to which the connective tissue was closely adherent. The outer margins of these had a fibrillar appearance. The edges of the hyaline matrix on the sides of the defect projected. The cartilage was faint-staining and showed fibrillation and was closely adherent to the connective tissue in these places. The connective tissue in these portions of the defect contained many cartilage cells (connective tissue cartilage). On one side of the defect, the cartilage was bent down over the cut edge of the calcified matrix in a hooklike projection. There was a dark-staining fibrous layer containing long fusiform cells which extended over the fibrous pannus of the defect and the cartilage on both sides. The continuity of this was not broken, and it was in no way connected with the underlying cartilage in structure. This was believed to be definitely a perichondrium.

Internal Condyle of the Femur.—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section showed only one portion of the defect. This portion was filled with loose connective

tissue which contained many blood vessels. The connective tissue was denser on the surface than toward the bony margin. It was closely adherent to the hyaline matrix on one side, but did not extend over the cartilage. The edge of the hyaline matrix was faint-staining compared with the normal hyaline cartilage farther away. There were many islands of pale-staining, disintegrating cartilage in the connective tissue pannus filling the defect. In the connective tissue adjacent to the bone were many cartilage cells and some areas of early fibrocartilage. The superficial layer of cartilage, which was nonnucleated, was stripped up for a short distance, but was not deeply stained as had been so often observed. There was no evidence of any fibrocellular layer which might be called a perichondrium.

Internal Condylar Ridge.—The cartilage was traumatized with a metal hammer. Gross examination was not made. The microscopic section showed the traumatized area. Most of the cartilage was covered by a rather thick fibrocellular layer which took a dark stain. The cells were long and fusiform. In one place, this fibrous layer, which was thought to be a definite perichondrium, was lifted up from the matrix and there it had a few red blood cells beneath it. The matrix here was of irregular contour and took an uneven stain. The border of cartilage not covered by the perichondrium showed fibrillation and disintegration. There was one long irregular break in the cartilage matrix, extending from the surface of the cartilage obliquely backward to the calcified matrix, the line of which it followed for a short distance. In the widest part of this cleft were many irregular sequestrations of cartilage with faint-staining matrix and cells, showing fibrillation about their borders.

External Condylar Ridge.—The cartilage was traumatized with a metal hammer. Gross examination was not made. The microscopic section showed clearly the traumatized portion of the ridge. A fibrous layer extended over the cartilage in the intercondylar space, ended at the beginning of the prominence of the ridge, and was continued again on the other side. This was believed to be a perichondrium. The cells in this were long and fusiform. The cartilage over the prominence of the ridge was somewhat disintegrated on the surface. Parallel to the surface, in the middle layers of the cartilage, was a cleft, which was thought to be due to the trauma. About this cleft, the cartilage took a distinctly lighter stain. There was no large amount of fragmentation of cartilage, and no new cartilage cells were seen.

EXPERIMENT 8.—The knee joint was used, and the defects were made with the scalpel and the burr in the patella, the external and internal condyles of the femur and the upper and lower intercondylar spaces. The condylar ridges of the femur were traumatized with a metal hammer. The dog was killed four weeks after the operation.

Patella.—The defect extended through to the calcified matrix. On gross examination, a thick sticky exudate was found covering the patellar surface of the joint. The microscopic section was not cut clearly through the denuded area. The incised area, however, was partially covered with fibrous tissue, which contained some cartilage cells. On one side of the defect a well formed area of fibrocartilage could be seen, with deeply stained cells and fibrils. In the fibrous pannus were some areas of hyaline matrix, which showed disintegration. Many blood vessels coursed through the fibrous pannus.

External Condyle of the Femur (Outer Side).—The defect extended through to the subchondral bone. Gross inspection showed it to be filled with granulation tissue. The microscopic section confirmed this observation and showed the presence

of fibrous tissue. A few areas of fibrocartilage were attached to the bone. The cartilage on this joint area was normally fibrocartilage. Hyaline cartilage was not seen. The fibrous pannus was well vascularized.

Internal Condyle of the Femur (Outer Side).—The defect extended through to the subchondral bone. On gross examination, the defect was found to be filled with granulation tissue. The microscopic section showed no hyaline cartilage. The defect was filled with granulation and fibrous tissue, containing many blood vessels. Fibrocartilage was seen along the edges of the calcified matrix and along the bone margin of the defect.

Upper Intercondylar Space.—The defect extended through to the subchondral bone. On gross examination, a thick, sticky joint fluid with granulation tissue filled the defect. The microscopic section passed clearly through the defect. The defect was filled with granulation tissue containing many blood vessels. On the surface of the defect, much fibrin and many pus cells were found, with one large organized mass. Pus and fibrin were also contained in the granulation tissue. The edges of the cartilage on both sides were well demarcated, but were pale-staining with fibrillation and disintegration. Some of the connective tissue adjacent to this cartilage contained cartilage cells. There were no new hyaline cartilage cells present. In the granulation tissue was an old, pale-staining, disintegrating nodule of cartilage which was being penetrated by the surrounding tissue. The connective tissue on one side of the defect extended for a short distance over the cartilage edge. The margin of the hyaline matrix showed some fibrillation and pale staining.

Lower Intercondylar Space.—The defect extended through to the subchondral bone. Gross examination showed a thick, sticky joint fluid, with the defect filled by granulation tissue. The microscopic sections showed the defect on one side of the cartilage. The defect was filled with granulation tissue containing many blood vessels. Pus and fibrin were found on the surface of the defect and extended over the edge of the hyaline cartilage. As the edge of the bone and cartilage was approached, the granulation tissue changed into fibrous tissue. This fibrous tissue contained some cartilage cells, and also some areas of typical fibrocartilage. The surface of the defect showed rather compact fibrous tissue with blood vessels, which was similar to a perichondrium. This, however, did not extend over the hyaline cartilage. It was thought that the section was probably cut in that portion of the intercondylar space which was adjacent to the border of the hyaline cartilage.

Internal Condylar Ridge.—The cartilage was traumatized with a hammer. On gross examination, a thick, sticky exudate was found in the joint, with a depression over the ridge. The microscopic section was clearly through the traumatized area. This area showed a depression into the bone with an absorption of cartilage, and resembled the areas made with a burr through to the subchondral bone. The defect in the cartilage was filled with granulation tissue containing a large amount of fibrin and pus. The surface of the granulation tissue, as well as the remaining cartilage, was covered with a thin layer of pus and fibrin. A fibrous layer covered the defect and continued for some distance over the cartilage on one side. The lower portion of this layer contained some cells that looked like elongated cartilage cells. On one margin of the defect, the hyaline matrix projected into the granulation tissue; this projection took a pale stain and showed disintegration and fibrillation. On the other margin of the defect was the same type of cartilage, which showed evidence of connective tissue having penetrated its outer border. On the surface of this hyaline matrix were large, well stained cells, which resem-

bled new cartilage cells. In the matrix were small spaces that resembled lacunae. There was a penetration of the granulation tissue filling the defect with connective tissue proliferating from the bone-marrow. The tissue in the defect was well vascularized. The surrounding bone did not take the normal stain and looked somewhat necrotic. The remarkable fact about the section was that the trauma from the hammer had caused so much destruction in the cartilage and underlying bone. With so much pus and fibrin there must have been infection. The picture was probably the result of the reaction to trauma and infection. Unfortunately, the joint fluid was not cultured.

External Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination showed a thick, sticky exudate in the joint, with a depression over the ridge. The microscopic section was cut through the traumatized area. As was the case in the internal ridge, there was a depression in the bone with an absorption of the cartilage over the ridge. This defect was filled with granulation tissue which contained a great many blood vessels. The cartilage was covered with pus and fibrin, which extended over the defect and down into the granulation tissue. The cartilage on the borders of the defect was pale-staining, showing faint nuclei and evidences of having been penetrated by connective tissue. There was much fibrillation of this matrix. The cartilage in this area did not take the normal stain. It was in this region that there was evidence of a fibrous coat covering the cartilage, which had extended from the outer margins. This was the only evidence of a perichondrium. In the granulation tissue close to the bone margin was an island of old cartilage which took a pale stain and showed faint nuclei and evidence of having been penetrated by the granulation tissue. In the cartilage matrix, several wide breaks were present, which were due to the trauma. There was a proliferation of the fibrous tissue of the bone-marrow up into the defect. The bone itself took an extremely poor stain and looked necrotic. The picture again was undoubtedly due to the trauma plus infection.

EXPERIMENT 9.—The knee joint was used, and the defects were made with the scalpel in the internal and external condylar ridges of the femur, the lower intercondylar space and the internal and external condyles of the tibia. The dog was killed four weeks after the operation.

Internal Condylar Ridge.—The defect extended through the superficial layers. On gross examination, definite evidence of healing was found. The microscopic section was cut through the maximum point of the ridge. Over the whole ridge, there was a thick fibrous coat, which contained elongated fusiform cells. In places, the outer margin of this showed a cellular layer similar to the synovial membrane. It was not certain whether this fibrous layer represented a perichondrium or was a manifestation of repair. No definite cartilage cells were seen in its lower layers, as were sometimes seen when a perichondrium was present. The cartilage itself took a rather pale stain and showed fibrillation on the surface. Some of the superficial cartilage cells were well stained and had a distended quadrilateral appearance. It was thought that these might represent an early stage of new cartilage cells. The line of the calcified matrix was irregular, and in places it had been penetrated by a proliferation of connective tissue from the subchondral marrow.

External Condylar Ridge.—The defect extended through the superficial layers. Gross examination showed some evidence of healing. The microscopic section was through the maximum point of the ridge. There was one small protrusion of cartilage, covered by fibrous tissue, which may have been a regenerative change. The edge of the matrix was slightly irregular and showed some disintegration

The superficial cartilage cells were faintly stained. Some black detritus was observed along the surface. One margin of the cartilage was covered by a fibrous layer containing blood vessels, which was an extension of the capsule.

Lower Intercondylar Space.—The defect was made through to the calcified matrix. Gross examination showed evidence of healing. The microscopic section was clearly cut through the defect. The defect had an irregular border on which the cartilage cells were of unusually large size. Superimposed on the cartilage margin was a layer of fibrous tissue, containing cartilage cells. This took a dark stain in places. At the terminal margin of the hyaline cartilage there was fibrous tissue containing cartilage cells and typical looking fibrocartilage. It was believed that this was normal for the marginal edge of the hyaline cartilage.

Internal Condyle of the Tibia.—The defect extended through to the calcified matrix. Gross examination showed definite evidence of healing. The microscopic section was not cut through the defect and could not be included in the analysis. There was one rather interesting observation: On the edge of the hyaline matrix, adjacent to the fibrous tissue was a well circumscribed and well demarcated blood space, which looked like a venule within hyaline cartilage.

External Condyle of the Tibia.—The defect extended through the superficial layers. Gross examination showed the defect to be well filled with fibrous tissue. The microscopic section did not show the area denuded. There was an extension of the fibrous tissue on one side over the hyaline matrix, which was the only evidence of a perichondrium. The most superficial layer of cartilage took a darker stain and contained elongated cells.

EXPERIMENT 10.—The knee joint was used, and the defects were made with the scalpel in the patella, the external and internal condyles of the femur and the external and internal condyles of the tibia. The condylar ridges of the femur were traumatized by pounding with a metal hammer. The dog was killed four weeks after the operation.

Patella.—The defect extended through the superficial layers. Gross examination showed evidence of healing. The microscopic section was clearly cut through the denuded area. Only the most superficial layers of cartilage were removed, about one fourth of the full thickness. There was a slight irregularity of the border of the defect. No new cartilage cells were observed. On one side, extending from the edge over the hyaline matrix for a short distance was a fibrous layer which contained some cartilage cells. This was the only evidence of a perichondrium. Along the margin of the matrix in one place, some elongated cartilage cells were seen, which were similar to a perichondrium.

External Condyle of the Femur.—The defect extended through the superficial layers. Gross examination showed healing, with fibrous tissue attached. The microscopic section was cut through the defect. Along the margin of the incised cartilage, pushing the hyaline matrix out, were one or two large cartilage cells which were suspected of being new cartilage cells, but they did not take a deep stain and were not multinucleated. There was a great deal of débris along the margin of the cartilage. On one margin, the fibrous tissue from the synovial membrane extended over a portion of the hyaline matrix. This was the only evidence of a perichondrium. This fibrous layer had some cartilage cells in its lower portions.

Internal Condyle of the Femur.—The defect extended through the superficial layers. Gross examination showed evidence of healing. The microscopic section

showed that about one half of the thickness of the cartilage had been incised. The margin of the incised cartilage was somewhat irregular with many faint-staining cartilage cells on the periphery. Along the superficial portion of the defect were some large quadrilateral cartilage cells which may have represented an early stage in the proliferation of new cartilage cells. On both lateral margins of the cartilage there was an extension of the fibrous tissue from the edges for a short distance. This fibrous layer contained some cartilage cells in the deeper parts. Blood vessels were seen in this perichondrium.

External Condyle of the Tibia.—The defect extended through the superficial layers. Gross examination showed evidence of healing, which was more marked than in a similar area in the internal condyle of the tibia. The microscopic section showed that the defect reached through about one third of the thickness of the cartilage. The defect showed an irregular and indented margin of cartilage. There was some débris along the edge. The edge of the matrix in the defect showed some disintegration, with a proliferation of oval and spindle cells in some places. In the superficial layers, were a few large quadrilateral cartilage cells, deeply stained. These were thought to represent new cartilage cells. In the cartilage was a cleft in which there was granulation tissue containing some spindle cells. The fibrous tissue on one margin extended over the hyaline matrix for a short distance. This was the only evidence of a perichondrium.

Internal Condyle of the Tibia.—The defect extended through the superficial layers (fig. 2). Gross examination revealed definite evidence of healing. The microscopic section showed that the defect extended through about two thirds of the cartilage. In the defect there was a proliferation of fibrous tissue, which extended into the matrix in two nipple-like processes. Spindle cells were present in the outer portion of this and oval cells, of cartilage type, in the deeper portions. In this deeper part were some areas of hyaline matrix which were adjacent to a pale-staining and fibrillating hyaline matrix of the main portion of the cartilage. The impression was that the edge of the matrix showing the disintegration had been replaced with cartilage cells in fibrous tissue. This new tissue had arisen from the necrosis of the old cartilage. No new cartilage cells were observed. There was no evidence of a perichondrium.

External Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination showed little evidence of the trauma. The microscopic section showed the maximum point of the ridge. The margin of the cartilage over the ridge was irregular, with indentations which contained fibrin, leukocytes and débris. A cleft extended down one half of the width of the cartilage. The calcified matrix beneath the ridge was broken in two places, and was irregular. In the cleft there was a proliferation of vascularized granulation tissue. Over the irregular margin of the cartilage, the cells were faint-staining, and the matrix showed some disintegration. Fibrous tissue extended over one margin of the cartilage for a short distance. This fibrous tissue was well vascularized. There was a proliferation of connective tissue from the bone-marrow up through the breaks in the calcified matrix. New cartilage cells were not observed.

Internal Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination showed little or no evidence of the trauma. The microscopic section showed the maximum point of the ridge. In the matrix over the ridge were some oblique breaks. Over the maximum point of the ridge, the edge of the matrix was irregular. There was some fibrillation of this edge, with a few leukocytes attached. From the lateral margin of the ridge, extending over the matrix, was a thick fibrous layer which terminated at the maximum point of the

ridge. Between these fibrous layers there was a protrusion of hyaline matrix and tissue. The outward portion of this had the typical appearance of hyaline cartilage, with matrix and cells, while the inner and central portion had a fibrillar appearance with spindle cells. Along the superficial margin of the cartilage were some lacunae which it was thought represented disintegrated cartilage cells. The cartilage cells were generally well stained. The protrusion of cartilage and fibrous tissue was believed to be a reaction to the trauma.

EXPERIMENT 11.—The knee joint was used, and the defects were made with the scalpel and the burr in the patella, the external and internal condyles of the femur, and the external and internal condyles of the tibia. The condylar ridges of the femur were traumatized by pounding with a metal hammer. The dog was killed two weeks after the operation.

Patella.—The defect extended through to the calcified matrix. Gross examination was not made. The microscopic section was not cut through the defect and could not be used in the analysis.

External Condyle of the Femur (Outer Side).—The defect extended through to the subchondral bone. No gross examination was made. The microscopic section was not clearly cut through the defect. Along the margin of the bone was some fibrocartilage which was covered by connective tissue. Hyaline cartilage was not seen.

Internal Condyle of the Femur (Outer Side).—The defect extended through to the subchondral bone. No gross examination was made. The microscopic section again was not clearly cut through the defect. In connective tissue attached to the bone, a few cartilage cells were seen. Hyaline cartilage was not found. The connective tissue was well dotted with blood vessels.

External Condyle of the Tibia.—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section was clearly cut through the defect. The defect did not contain fibrin or granulation tissue. The edges of the cartilage on both sides showed some fragmentation, with fibrillation of the matrix. The matrix and cells along this border both took a pale stain. In places, the hyaline matrix had loosened from the calcified matrix. This was probably due to the fixing and cutting of the section. Over the hyaline matrix for a short distance on one margin there was a fibrous layer, which was the only evidence of a perichondrium. The superficial edge of most of the cartilage showed elongated cells, which in places took a dark stain and resembled a perichondrium.

Internal Condyle of the Tibia.—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section was clearly cut through the defect. The defect was well filled with granulation and connective tissue. On one side of the defect, pale-staining cartilage projected into the granulation tissue. The edges of this showed fibrillation and were intimately connected with the loose connective tissue. Cartilage cells in the connective tissue extended from the projection of cartilage down into the defect. Several pale-staining, disintegrating islands of cartilage were present in the granulation tissue on the superficial side. The tissue in the defect was well filled with blood vessels. The bone in places was faintly stained. The palely stained edges of the cartilage and the connective tissue in the defect were in sharp contrast with the more heavily stained normal cartilage.

External Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination was not made. The microscopic section showed the ridge

clearly. At the maximum point of this ridge, there was a break in the cartilage in its superficial portion. In addition there were several other oblique breaks running into the matrix. Fibrin was found in some of these clefts in the cartilage. The edge of the matrix was irregular, with the cells and the matrix taking a faint stain. There was one large piece of cartilage which looked as if it was about to be broken off. The connective tissue of the bone-marrow had proliferated into the hyaline matrix in places. On the outer margin of the cartilage was a short extension of fibrous tissue which contained blood vessels and was the only perichondrium present. A dark-staining superficial layer of cartilage was seen in places, which was nonnucleated. This appeared to be a perichondrium.

Internal Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination was not made. The microscopic section showed the traumatized area clearly. Over the maximum point of the ridge, there was a depression in the matrix, which took a pale stain. The matrix also showed fibrillation of the margin, and a break in the cartilage down toward the bone. This was believed to be due to the trauma. There was some cell detritus over the margin of the matrix in the traumatized area. Fibrous tissue extended over the cartilage from the outer margin and terminated at the beginning of the traumatized area. The lower portion of this contained some elongated cells that looked like cartilage cells. This was the only evidence of a perichondrium.

EXPERIMENT 12.—The knee joint was used, and the defects were made with a scalpel in the patella, the external and internal condyles of the femur, the condylar ridges of the femur, the lower intercondylar space of the femur and the external and internal condyles of the tibia. The dog was killed two weeks after operation.

Patella.—The defect extended through to the calcified matrix. Gross examination was not made. The microscopic section was clearly cut through the defect. The margin of the defect was somewhat irregular and had some detritus adherent to it. The cells along the margin were generally well stained. In places, however, the matrix and the cells took a poor stain. On one side of the incised area was a folded back piece of fibrous membrane which had long fusiform cells that looked like perichondrium, but this could not be traced over the margin of the cartilage. The cells along the margin of the cartilage not in the defect were elongated. There was an extension of a fibrous membrane over the margin of the cartilage from the edge for a short distance. It was the only perichondrium present.

External Condyle of the Femur.—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed the incised area clearly. This defect had a fairly regular margin and contained fibrin and leukocytes. In places, the fibrin looked as if it was undergoing organization, there being some long fusiform cells present.

There was considerable cell detritus between the fibrin and the hyaline matrix. One budding cartilage cell along the edge looked as if it might be a new cartilage cell. In places, the superficial cartilage layer was deeply stained and contained elongated cells parallel to the surface. The synovial membrane was reflected for a short distance over the cartilage on one edge. This was the only evidence of a perichondrium.

Internal Condyle of the Femur.—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed only the most superficial layers denuded. This defect was small and the margin of the matrix was regular. New cartilage cells were not present. On one border

of the cartilage, a fibrous layer could be seen for a short distance, which contained blood vessels showing injection. This was the only evidence of a perichondrium. The defect contained a small amount of fibrin. Some of the cells and the matrix on the outer margin were faintly stained.

Condylar Ridges of the Femur.—The defects extended through the superficial layers. No gross examination was made. The microscopic section showed the defects in both ridges clearly. The section was cut obliquely so that the cartilage of the epiphyseal line was continuous with the cartilage of the surface on the inner side. The edges of the defects were slightly irregular, with evidence of disintegration, and had some fibrin and débris adherent to them. In the cartilage matrix were some breaks which contained fibrin. The edges of the cartilage took generally a deeper stain and in places had a fibrillar appearance. This was not present over the maximum points of the ridges. There was a projection of fibrous tissue over the cartilage matrix on the edges for a short distance; it was the only evidence of a perichondrium.

Lower Intercondylar Space.—The defect extended through to the calcified matrix. No gross examination was made. The microscopic section did not show the defect clearly. The section contained mostly cancellous bone. A few pieces of pale-staining hyaline cartilage were present on the surface of this bone. In places, the connective tissue on the outer border of the bone had penetrated the bone-marrow.

External Condyle of the Tibia.—The defect extended through the superficial layers (fig. 1). Gross examination was not made. The microscopic section showed the defect clearly. The defect was fairly well filled with loose connective tissue and granulation tissue, which appeared to have proliferated in part from the fibrous tissue on one side of the defect. From the edge of the defect there was a proliferation of an area of new fibrocartilage which was surrounded by connective tissue. The cell columns in the deeper layers of cartilage on one side had definitely started to turn their lines of axis toward the defect. This gave them the appearance of leaning toward the defect. Considerable fibrin was seen in the granulation tissue. The edge of the cartilage in the defect took a faint stain and showed evidence of disintegration. Over the cartilage on one border for a short distance was an extension of the synovial membrane which was the only evidence of a perichondrium.

Internal Condyle of the Tibia.—The defect extended through the superficial layers. Gross examination was not made. The microscopic section was cut to one margin of the defect and did not represent a true picture of the condition. The cartilage in no place looked like typical hyaline cartilage. Fibrils ran through most of it. There was one large area of fibrous tissue containing cartilage cells overlying an area of hyaline cartilage. This looked like a little hillock on top of the cartilage. None of the cartilage took a normal stain. There was no suggestion of a perichondrium.

EXPERIMENT 13.—The knee joint was used, and the defects were made with the scalpel in the patella, the external and internal condyles of the femur, the upper intercondylar space of the femur and the external and internal condyles of the tibia. The condylar ridges of the femur were traumatized with a metal hammer. The dog was killed one week after operation.

Patella.—The defect extended through to the calcified matrix. On gross examination, the denuded area looked unchanged. The microscopic section showed all the cartilage to have been removed from the patella, except small bits on either

margin. There was no evidence of the formation of fibrin. Fibrous tissue extended over the edges of the remaining hyaline matrix for a short distance.

External Condyle of the Femur.—The defect extended through to the calcified matrix. Gross examination showed no change in the denuded area. The microscopic section showed that only a small amount of hyaline cartilage was attached to the bone. There was some formation of fibrin in one place. Along the margin were a great many small sequestrations of cartilage and bone which showed evidence of disintegration and took a faint stain. The edge of the hyaline cartilage was irregular, but took a good stain.

Internal Condyle of the Femur.—The defect extended through to the calcified matrix. Gross examination showed no change. The microscopic section showed an irregular margin to the defect in the calcified matrix. The edge of the cartilage took a fainter stain than normal, and showed fibrillation. Some fibrin was attached. There were several small pieces of cartilage along this margin, and also some bits of cartilage with bone attached. One of these had reattached itself to the calcified matrix with fibrin. Over the cartilage for a short distance on one side was an extension of a fibrous membrane, which was the only evidence of a perichondrium.

Upper Intercondylar Space.—The defect extended through the superficial layers. Gross examination showed no change in the denuded area. The microscopic section showed the denuded portion. The edge of this was unusually regular, but showed fibrillation and took a paler stain than normal. Along the margin were some cartilage capsules, which had lost their nuclei. Some débris was adherent to the surface.

External Condyle of the Tibia.—The defect extended through the superficial layers. No change was observed in the defect on gross examination. The microscopic section showed the incised area clearly. There were some superficial cartilage cells which were distinctly larger and took a deeper stain than the normal ones. Most of the margin of the cartilage took a lighter stain than normal. These cells looked like new cartilage cells. Some of the superficial cells appeared to have lost their nuclei and had only the capsule forms left on the margin. There was one transverse cleft in the cartilage down to the calcified matrix, the borders of which showed some fibrillation.

Internal Condyle of the Tibia.—The defect extended through the superficial layers. Gross examination showed no change in the defect. The microscopic section was poorly stained and fixed. There were so many artefacts that it was impossible to tell what were the true cartilage changes.

External Condylar Ridge.—The cartilage was traumatized with a hammer (fig. 7). Gross examination showed a depression in the ridge made by the trauma. The microscopic section showed the traumatized area clearly. A depression in the cartilage over the maximum point of the ridge was filled with fibrin. This fibrin also extended for a short distance over the margin of the cartilage on one side. There were several clefts in the cartilage partially filled with fibrin. The underlying calcified matrix was broken and depressed inward over the indentation on the margin of the cartilage. The underlying bone also showed some fragmentation. All these changes were believed to be due to the trauma. The edge of the matrix was of a paler stain than the normal, and some of the cells showed evidence of disintegration. This edge, however, was fairly regular. Over one side of the cartilage for a short distance was a fibrous layer, which was the only sign of a perichondrium.

Internal Condylar Ridge.—The cartilage was traumatized with a hammer. Gross examination revealed evidence of the trauma. The microscopic section showed only the margin of the defect. The edge of the incised cartilage was irregular and faint-staining and had some detritus attached. Extending over one edge of the cartilage was a fibrous membrane, which was a perichondrium.

EXPERIMENT 14.—The knee joint was used, and the defects were made with a scalpel in the patella, the external and internal condyles of the femur, the condylar ridges of the femur, the lower intercondylar space and the external and internal condyles of the tibia. The dog was killed one week after the operation.

Patella.—The defect extended through the superficial layers. In the gross examination no change was noted. The microscopic section showed the defect clearly. The defect was not filled with fibrin. The edge was fairly regular, but the matrix and the cells took a lighter stain than normal. Along the cut margin were several large and deeply stained cells which were suspected of being new cells. There were some areas of a deeply stained, nonnucleated superficial layer of cartilage. On one edge the synovial membrane was reflected over the cartilage for a short distance; this was the only evidence of a perichondrium.

External Condyle of the Femur.—The defect extended through the superficial layers. In the gross examination, no changes were seen. The microscopic section showed the denuded area to be well demarcated. There was an irregular margin, with some fibrillation and disintegration of the cartilage matrix. Along the surface, considerable débris and disintegrating cartilage cells were seen. The superficial layer of the cartilage in places was deeply stained, with small fusiform cells parallel to the surface. No perichondrium was present.

Internal Condyle of the Femur.—The defect extended through the superficial layers. Gross examination showed no change. The microscopic section showed the defect clearly. The edge of the cartilage was fairly regular, with considerable débris of disintegrated cells along the margin. The superficial layers of the cartilage were slightly less stained than the underlying layers. The synovial membrane was reflected over the cartilage for a short distance on one margin; this was the only evidence of a perichondrium.

Condylar Ridges of the Femur.—The defects extended through the superficial layers. The gross examination showed the defects unchanged. The microscopic section showed the defect in the external ridge to be well demarcated, but the defect in the internal ridge to be broken, owing to the poor preparation. Some fibrin and débris were seen along the borders of the cartilage, especially over the outer defect. The cartilage cells and matrix were generally well stained. Over the cartilage on one margin, for a short distance, was a proliferation of a fibrous layer which was the only evidence of a perichondrium.

Lower Intercondylar Space.—The defect extended through to the calcified matrix. The gross inspection showed the defect to be unchanged. The microscopic section was cut below the defect in the popliteal space. The space between the condyles showed no hyaline cartilage. In this space, fibrocartilage was attached to the bone on one side, and cellular connective tissue, on the other. Some fibrin was present along the margins of the hyaline cartilage. On one border of the hyaline cartilage, there was a reflection of the synovial membrane for a short distance, which was the only evidence of a perichondrium.

External Condyle of the Tibia.—The defect extended through the superficial layers. The gross examination showed no change in the defect. The microscopic

section showed the incised area to be fairly well demarcated. In this area were some fibrin and débris. In the cartilage was a break which showed a lighter staining matrix lining one side, with a scarcity of cartilage cells in this light matrix. There was a reflection of the synovial membrane for a short distance over the cartilage on one margin; this was the only evidence of a perichondrium.

Internal Condyle of the Tibia.—The defect extended through the superficial layers. The gross examination showed no change in the incised area. The microscopic section was poorly cut and showed a great number of breaks in the cartilage. The margin of the defect was irregular and had some débris attached. The cartilage cells and the matrix were poorly stained. There was no evidence of a perichondrium.

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